FILE DESCRIPTION

PHILADELPHIA FILE

SUBJECT HARRY GOLD

FILE NO. 65-4307

VOLUME NO. 1-B-14

SERIALS —

NOTICE

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Inventory Worksheet
FD-503 (2-18-77)

VOLUME Bulky PHILADELPHIA FILES

INVENTORIED BY ckk

REVIEWED BY DP

File No: 65-4307-1-B-14 Re: Harry Gold

Date: 5.30.78 (month/year)

Serial	Date	Description (Type of communication, to, from)	No. of Pages Actual	No. of Pages Released	Exemptions used or, to whom referred (Identify statute if (b)(3) cited)
1-B 14	6.6.50	FO 141 Bulky Exhibit Items 1-5	1	1	
Enclosure #1	6.6.50	Envelope	2	2	
—	6.6.50	Mothproofing notes	4	4	some parts are illegible
—	6.6.50	Butylene Glycol notes	1	1	
—	6.6.50	Belle Meade letterheads	2	2	
Enclosure #2	6.6.50	Envelope	1	1	
-	6.6.50	Chemical analysis	21	21	
- Enclosure #3	6.6.50	Folder	1	1	
-	6.6.50	Photocopies & cover sheet	8	8	
-	6.6.50	Notes on Nicotinic Acid	18	18	
Enclosure #4	6.6.50	Envelope	1	1	
-	6.6.50	Notes on Pantothenic acid	39	39	

FBI/DOJ

Inventory Worksheet
FD-503 (2-18-77)

VOLUME Bulky PHILADELPHIA FILES

INVENTORIED BY ckk

REVIEWED BY _____

File No: 65-4307-1-B14 Re: Harry Gold

Date: 3/78 (month/year)

Serial	Date	Description (Type of communication, to, from)	No. of Pages Actual	No. of Pages Released	Exemptions used or, to whom referred (Identify statute if (b)(3) cited)
—	6.6.50	Photocopies	41	41	
—	7.15.46	Ltr. Aircraft Corp to A. Brotman and accom.	1	1	
Enclosure #5	6.6.50	Folder & Envelope	2	1	
—	6.6.50	Notes on Pyridoxin	52	52	
—	6.6.50	Photocopies	31	31	

FBI/DOJ

(7-1-48)

BULKY EXHIBIT

1

Date received June 6, 1950

HARRY GOLD

ESPIONAGE - R

(Title of case)

Submitted by Special Agent ROBERT E. MASTERS

Source from which obtained SEARCH OF SUBJECT'S RESIDENCE

Address 6823 Kindred St., Phila

Purpose for which acquired Aid in investigation

Location of bulky exhibit Bulky Exhibit Room

Estimated date of disposition 12-1-50

Ultimate disposition to be made of exhibit to be determined

List of contents:

Envelope, brown manila marked Re-org 3-29-46 from Harry Gold's bedroom
Envelope, brown manila, marked Re-org 3-29-46
Manila folder marked Photocopies Nicotinic Acid
Manila folder marked Pantothenic Acid
Manila folder marked Nicotinic Acid

Return 5/31/55 RS

Return 11/14/55 RS

Return 11/16/56 RS

Return 6/7/56

65-4302-1-B-14

FBI - PHILADELPHIA
JUN 22 1950

#1

June 6, 1950

Joseph Gold

(Name of Contributor)

6823 Kindred St., Philadelphia Pa.

(Address of Contributor)

By Robert J. Wechsler

(Name of Recipient)

To Be Returned: Yes / No

Description: 1 envelope, brown, manila, marked Re-Org 4/24/50 from Harry Gold - Hebron

File No. 65-4307-1-B-14

Re-orig 3-2-9-46

1. Bills made out to order

2. Bills to be made out in duplicate

3. Don't make out forms N etc.

I

Mothproofing — In recent years the mothproofing of wools and worsteds has gained in importance because of the discovery of effective chemical compounds and more simple applications. There is a definite place for satisfactory mothproofing for all wool goods which are stored during certain periods of the year, such as wearing apparel and blankets. This need is also desired in upholstery, carpeting and other bulky materials, which once infested can only be fumigated.

While there are many compounds recommended for this purpose there are only a few which are really effective over a long period of time. For treatment by the woolen manufacturer the following types of compounds have found commercial application — Rotenone — Silans — Silico-fluorides — Thiuram disulfides — Mitick — only chemical tested

Assumes - 51

directions in the fabric which is infested - It has also been reported as destroying books

Clothes Moths (Tinea pellionella & Tineola bisselliella (Humm.))

feed on wool - fur - hair - feathers and all fabrics made from them. They also feed on matter such as dead insects, etc

life cycle

egg - larva, the pupa and the moth.

The moth or miller which is the adult seldom lives as long as one month - usually dies between the 7th and 14th day after the emerge from the pupa - they do not take nourishment

The female moths start laying eggs before they are fully 1 day old and usually lay eggs each day of their life - When she stops laying eggs at most she will die in a day or so. She lays about 100 to 150 eggs and ½ of the number in the first few days of her life.

6/6/70

II

Tests made by Springle and Clabaugh disclose that Silico-fluoride effective as initially applied to fabrics, are not removed by dry cleaning solvents and are not deteriorated by light - however they are removed by washing

Chinchona alkaloids and Paterone are effective as initially applied to the fabrics, are not removed by washing but are removed by dry cleaning solvents and are deteriorated by exposure to light

Eulan C N and Eulan N K are produced by General Dyestuff Corp and can be applied to piece goods during dyeing process they are not removed by washing dry cleaning deteriorated by exposure to light they are effective as initially applied to fabric

Carpet Beetle — (called "Buffalo Moths")
(they get in wall spaces and hide during cleaning operations)
1 - Common Carpet Beetle - (Anthrenus scrophulariae L.)
2 - Furniture Carpet Beetle - (A. vorax = voracious)
3 - the Varied Carpet Beetle (A. verbasci L.)
4 - Black Carpet Beetle (Attagenus piceus - Oliv.)
none more than 1/4 inch - adults are hard shelled - oval.

Only larvae or grubs of carpet beetle cause damage —

the larvae shuns light and gets in dark places - particularly articles lying in storage and about the edges of carpets and under baseboards)

Moths – Common species of clothes moths

There are 3 very common species –

1-Case-making clothes moth – (Tinea pellionella L)

2-Webbing clothes moth (Tineola bisselliella – Hummel)

3-Tapestry moth – (Trichophaga tapetzella L)

1-Tinea pellionella L – wing spread ½ inch, head a grayish yellow or buff – wings are white and silky (Called case making because the larva forms protection, makes a portable case out of spun silk and fragments of the fabric on which it feeds) – the larva almost never leaves its case – When resting it goes in completely – when eating or moving about it merely protrudes its head – the larva spins almost invisible webs on the fabric on which it feeds and is more likely to crawl about. Heedlessly, eating small holes.

Webbing moth – (Tineola bisselliella – Hummel) same size as above – but color is uniformly pale buff – no spots – never over ½ inch usually smaller

the webbing moth is most abundant and really injurious to clothes in the last few years nearly all the damage reported from 19 of 21 places in the North Chicago district have been caused by the species. The larva of the webbing clothes moth resembles that of the case making moth - but it does not make a portable case - it spins a silky tunnel or tunnels wherever it goes. The larva is covered by mass of silken threads as random the larvae may be quite restless and often may be seen crawling over fabrics or upholstery at full growth it spins a cocoon and in this cocoon the transformation from larva to adult [redacted] takes place, as in the case in the species the Chr[redacted] bores its way partly out of the cocoon so the moth is about to emerge

Tapestry moth (Trichophaga tapetzella L.)
(not common in U.S. as the above) two and one-half
larger (3/4" long) and colored - head is black - and
prefer heavier fabrics - (carpets - horse blankets, furs, felting &c.
the larvae construct burrows or silk tubes gallerie in old

Station Lab Rhodia

Core = 30.0%

Tube = 6.2 cc

pH 5.4

Sp. Gr. 1.212/20°C

Iron 5 ppm

Copper 4.5 ppm

Ash Trace

Di Thio glycolic acid 18%

Thioglycolic None

Di thio glycolide None

Color Dk. Yellow

Sam #2
6/6/52

300
1600

2,3 - Butylene Glycol

organism - Aerobacter aerogenes
(A. aerogenes No. 199)

Inoculum for Fermentation

0.5% corn steep liquor
0.5% calcium carbonate
5% glucose

Inc. 3 - 5% Potato

Reducing sugar conc. 12.0 gm / 100 cc
Fermentation time 43 hrs

Fermentation medium / liter

3 gm. KH_2PO_4
3 gm. Urea
5 gm. $CaCO_3$

Look for: Northern Regional Lab. article
Dec. 1945 1189.

DISTILLERY PERMIT NO. 5D12

VA. A. B. C. LICENSE NO. 852

Belle Meade Distilling Corporation

DISTILLERS

BELLE MEADE, VIRGINIA
TELEPHONE: MARSHALL 4581

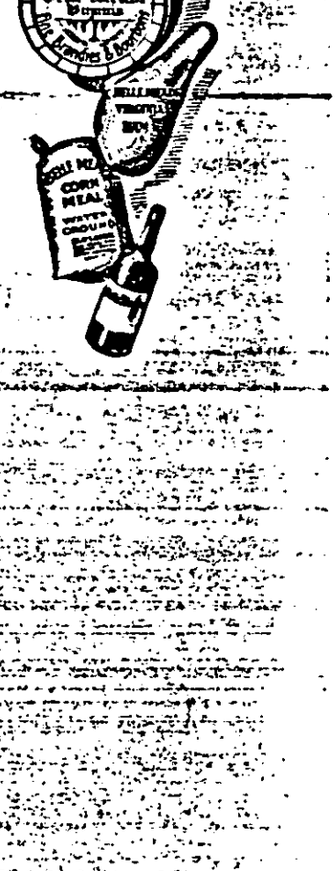
Exh. #2
6/6/50

Belle Meade Farms

BELLE MEADE, VIRGINIA

PHONE MARSHALL 4561

OWNED & OPERATED BY
Harry Greiske



Dr. Simon L. Miller

% Hotel Statler

Wash., D.C.

#2

Received June 6, 1950

From Joseph Gold
(Name of Contributor)

6823 Kindred St. Philadelphia, Pa.
(Address of Contributor)

By Robert E. Master
(Agent or Special Agent)

To be Returned Yes ( ) No ( )

Description of Enclosure Envelope, Return Receipt Requested, Postmarked 3:30 PM 3/29/50

File No. 65-4307-1B-14

Quantitative Chemical analysis

I Concentrations of materials

II Gravimetric analysis

III Volumetric analysis

IV Gas analysis

Quantitative anal. — what is in a certain material

steel — % C

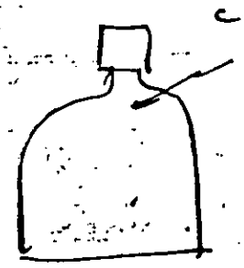
Stainless — % Ni - Cr

air — % carbon monoxide

whiskey — % fusel oil

I Concen. of materials

Sulfuric acid



commercial acid
94 % by wt.
1.84 Sp. Gr.

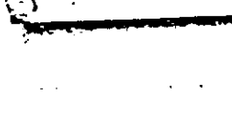
1000 gallons of 50 % by wt.

How many ~~gallons~~ lbs. of strong acid
→ 1000 gallons of 50 % by wt.

$410 \times 0.92 = 36.8$ g. NaOH

$\frac{36.8}{40} = 0.920$ N = NaOH.

$\frac{410 \times 0.02}{53} = \frac{0.015 \text{ N as } Na_2CO_3}{0.935 \text{ N}}$



(2)

1 cc

 of H_2O = 1 gm. at 4°C

1 cc of H_2SO_4 Density = wt/cc. at a definite temp.

 = 1.84 gms. at 60°F

1000 gals. × 3785 = 3,785,000 cc

cc's/gal.

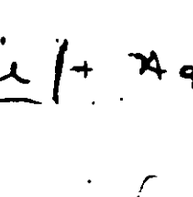
3785

3,785,000 × 1.526 = gms. of 50% acid

gms of 50% acid × 0.50 = gms. pure H_2SO_4

Exam #1
CGM
6/16/50

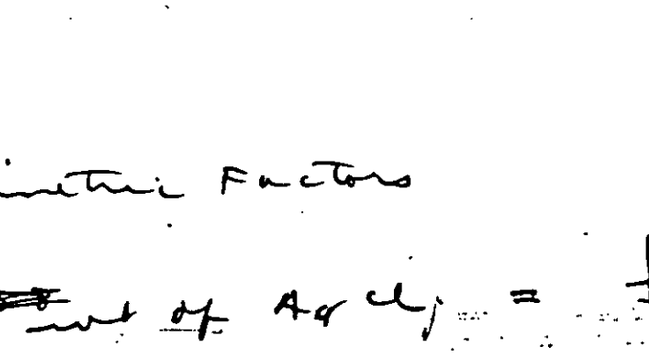
Gravimetric analysis



gms./cc
gms./gallon

$NaCl + AgNO_3 \longrightarrow AgCl + NaNO_3$

1 mole



AgCl

23
35
58

Gravimetric Factors

$\frac{\text{gNaCl}}{\text{gAgCl}} \times \text{wt of AgCl} = \text{wt of NaCl}$

1.2067 gms

Sought / Weighed × amt weighed = amt. sought.

NaCl : AgCl = wt of NaCl : wt of AgCl

$\frac{NaCl}{AgCl} \times \text{wt of AgCl} = \text{wt of NaCl}$

Sept #1
6/6/50

SO_4^{2-}

$Na_2SO_4 + BaCl_2 \xrightarrow{HNO_3} \underset{\text{white ppt}}{BaSO_4} + 2NaCl$ (1.5264)

Gravimetric Factor

(formula weight) × amt weighed = amt sought.

(gravimetric factor)

$\frac{Na_2SO_4}{BaSO_4} \times 1.5264$ gm.

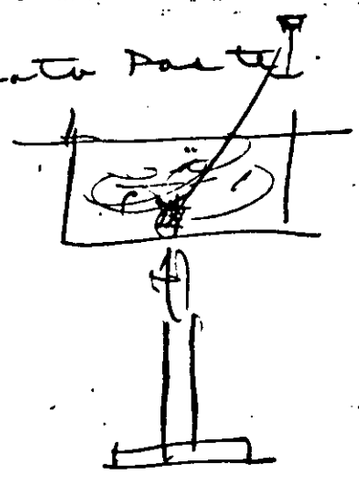
$\frac{0.6086}{14 \times 9} \times 1.5264 =$ gm. Na_2SO_4

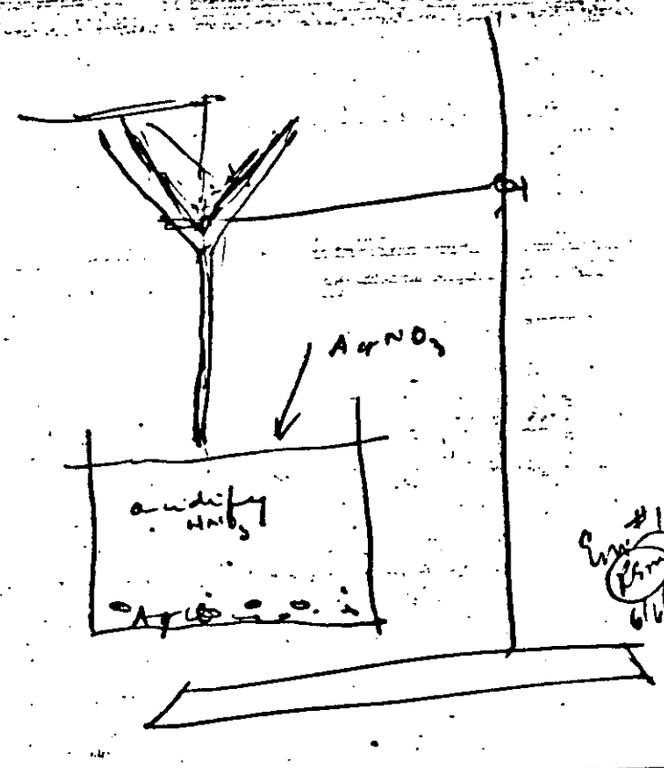
$\leftarrow 33.4$

1 gm of a mixture | gm of NaCl | % of NaCl

NaCl

Tomato Paste





⑥

0.0070 gm. NaCl

Equivalent weight × gm. equivalent = gm. NaCl

Gram Factor = 0.0070 gm. = gm. NaCl

0.408 × 0.0070 gm. = 0.0029 gm. NaCl

0.408
0.0070
0.00285 #60

% by wt of NaCl

gm. NaCl / 100 gm. paste

lbs. NaCl / 100 lbs. paste

$\frac{0.29}{1} \times 100 = 0.29$ % NaCl by wt

$\frac{\text{gm. Found}}{\text{gm. Weighed}} \times 100 =$ % by wt

0.29 lbs. NaCl

454 × 0.29 =

#1
6/6/15

ordering operations of quant. chemical analysis

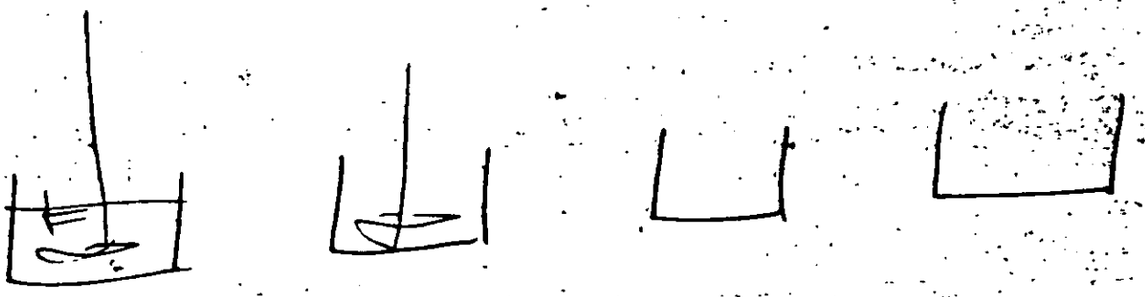
1. Solution

NaCl 3 g./100 cc

$NaIO_4$

a. use Handbook for solubilities

$KMnO_4$



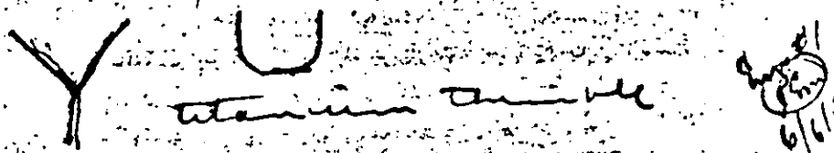
3 g/100 cc

.01

.2 g/liter

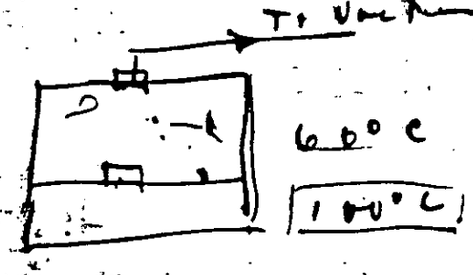
2. Prep. – set directions from book

3. Filtration – Fluted

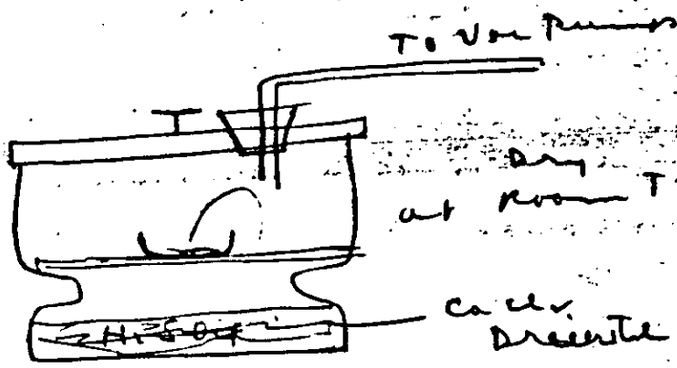


6/6/

Drying of Precipitate



Vac Drying thru Dessication



overnight

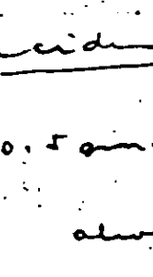
Reweighing

Volumetric analysis

Vol. anal. is easier + faster than grav. anal.

Pipet
Buret
VM. Flask
analytical balance

Primary Stds



0.1 N Thiosulfate $Na_2S_2O_3$

0.1 N NaOH

acidimetry & alkalimetry

Boric 0.5 gm. NaC_2O_3 (dry & purified)

always used with a definite amount of acid (HCl H_2SO_4)

Boric 0.2 NaOH

Benzoic acid (U.S. Bureau of Stds)
K acid Phthalate (Bureau of Stds)
Constant boiling HCl.

Oxidation & Reduction Stds

0.1 N Iodine
0.1 N Thiosulfate } use $K_2Cr_2O_7$ as std

$Ce_2(SO_4)_3$ Use in Stds

$KMnO_4$ 0.1 N { Ferrous ammonium sulfate
Dry $Na_2C_2O_4$ (sodium oxalate)

Quinn 6/6/15

Normality of solns.

a 1 N soln. of anything (acid, base, oxidizing agent, reducing agent) contains 1 eq. wt. in grams of the reacting substance.

i.e., to know how to make up a 1 N soln, the reaction must be known before the Normality can be calculated.

$$\underset{\text{1 eq. reacting wt.}}{HCl} + \underset{\text{40 gms/l.}}{NaOH} \rightarrow H_2O + NaCl$$

36.5 gms/l → 1 N soln

$$\underset{\text{98}}{H_2SO_4} + 2NaOH \rightarrow 2H_2O + Na_2SO_4$$

1 N of NaOH is still 40 gms/l.

$$\underset{\text{49}}{\tfrac{1}{2}H_2SO_4} + NaOH \rightarrow H_2O + \tfrac{1}{2}Na_2SO_4$$

$\frac{98}{2} = 49$ ← H_2SO_4/liter

$$\underline{H_3PO_4} + 3NaOH \rightarrow 3H_2O + Na_3PO_4$$

3

1 c.c. of any 1 N acid
= 1 c.c. of any 1 N base

HAc
HCl
H_2SO_4 and oxidizing agent
$Ca(OH)_2$
$Ba(OH)_2$
KOH
NaOH
T.E.A.

6/6/50

Basic Rule for Vol. analysis

cc × N = milliequivalent = gm of std substance we are looking for

cc of reacting soln.

milliequivalent wt of std substance = wt of std substance in 1 cc of a 1 N soln.

Ex. ___ soln of acid N? ___ HCl

Suppose ___ (0.5 gm) ___ Na_2CO_3

0.5000

M.O.

30.26 cc to titrate. What is N of acid

cc × N = milliequivalent = gm of std substance

cc × N = 0.5000

30.26 × N = 0.053

$Na_2CO_3 + 2HCl \rightarrow 2NaCl + CO_2 + H_2O$

$\frac{1}{2}Na_2CO_3 + HCl \rightarrow \frac{1}{2}NaCl + \frac{1}{2}CO_2 + \frac{1}{2}H_2O$

Mwt of Na_2CO_3 / 2 = $\frac{106}{2}$ = 53 gm / l → 1 N soln.

1 cc = $\frac{53}{1000}$ = 0.053 gm

6/6/57

(11)

~~Some of 0.053 = N_s = 0.500~~

$1.603 \times N_s = 0.5000$

$N_s = \frac{0.5000}{1.603}$

$N_s = 0.3119$ N

Equivalent Volumes of different solns.

HCl

HCl 0.1026 N

0.0832 N

25 cc

Do you need sum for all 10 titrations

10 determ

What must be found out, is how many cc of 0.0832 N HCl for each titration

If it takes 25 cc of 0.1026 N to do the job, then it should take more than 25 cc of 0.0832 N to do the same work

So, $\frac{0.1026}{0.0832} \times 25 = 30.87$ cc / titration

Then,

for 10 titrations

$30.87 \times 10 = 308.7$ cc

6/6/50

~~1.603 x 0.653~~ , N_s = 0.500

1.603 x N_s = 0.5000

$N_s = \frac{0.5000}{1.603}$

N_s = 0.3119 N

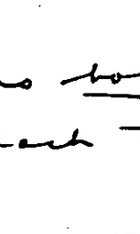
Equivalent Volumes of different solns:

HCl

HCl 0.1026 N

25 cc

10 determs



HCl 0.0832 N

Do you have enough for all 10 titrations

What must be found out, is how many cc of 0.0832 N HCl for each titration

If it takes 25 cc of 0.1026 N to do the job, then it should take more than 25 cc of 0.0832 N to do the same work

$\frac{0.1026}{0.0832} \times 25 = 30.87$ cc / titration

Then,

for 10 titrations

30.87 x 10 = 308.7 cc

#1

6/6/19

(12)

NaOH (0.2030 N) (acid)

(32.62) cc.

(KOH)

(12.50 cc)

What is N of KOH

∴ KOH is stronger & N of KOH must be > N of NaOH

$$\frac{32.62}{12.50} \times 0.2030 = 0.529 \text{ N KOH}$$

You have a 0.4186 N acid H_2SO_4

It takes ~ 8.31 cc for a titration

This figure is so small, that any error in reading → a > error in results

So, you want to dilute the acid so that it will take at least 40 cc for the same titration. What then will be the N of the acid?

$$\frac{8.31}{40.0.0} \times 0.4186 = 0.0868 \text{ N}$$

$$V_1 N_1 = V_2 N_2$$

$$\frac{8.31 \cdot 0.4186}{40} = N_2$$

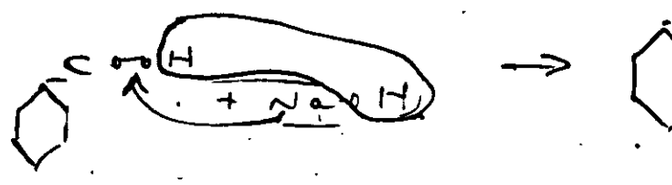
#1 (PSM) 6/6/50

(13)

You have an approx. 0.2 N KOH
you want to standardize it with benzoic acid
you should use between 25 & 40 cc. for
the standardization (to cut down any error
in the method or the reading of the buret).
What wt. of benzoic acid should you
use?

cc's × N's = mil's = gms of

40 × 0.2 × 0.1221 = gms of C_6H_5COOH



So, gm. equiv of C_6H_5COOH : $\frac{\text{benzoic acid}}{1} = \frac{122.1}{1}$ g./lit

$= \frac{122.1}{1000} = 0.1221$ g. = mil's

So) gms = 0.977

0.9 1.0

0.8

(14)

making up Std. Solns. of acids

0.1 N H_2SO_4 - how prepare?

Need

49 gms./l → 1 N H_2SO_4

So, 4.9 gms./l → 0.1 N H_2SO_4

Take regular strong (conc.) H_2SO_4

on label

1.84 Sp. Gr.

94 - 95 %

cc conc. × Sp. Gr. × % pure acid = gms pure acid

1 × 1.84 × 0.95 = 1.75 gms H_2SO_4/cc

we want 4.9 gms.

So, $\frac{4.9}{1.75}$ = 2.8 cc conc acid/l

→ 0.1 N soln.

Usually 3 cc is used with a pipet due to acid clinging to the side

For HCl, say a 0.5 N soln.

HCl is gas.

Hydrochloric acid is the gas dissolved in H_2O.

1.19 Sp. Gr.

38 %

Expt #1
BSR
4/6/37

(15)

Need:

36.5 gms. HCl / l → 1 N

3.65 gms. HCl / l → 0.1 N

or

36.5 × 0.5 = 18.25 gms. / l → 0.5 N

1 cc of HCl (conc.) =

cc acid × Sp. Gr. × % acid = gms. pure acid

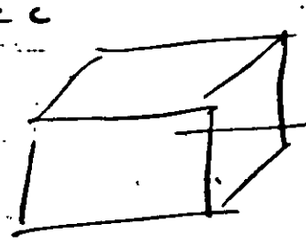
1 × 1.19 × 0.38 = 0.414 gms. pure HCl / cc

So, for 0.5 N gms. HCl / l of 0.5 N

$\frac{18.25}{0.414}$ = 43.1 cc.

gms. pure HCl / cc

$\frac{\text{gms.}}{\frac{\text{gms.}}{\text{cc}}}$ = gms × $\frac{\text{cc}}{\text{gms}}$ = cc



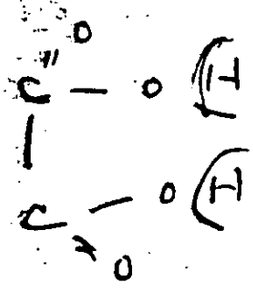
18.25 gms. pure HCl Needed
? cc. Needed

0.414 gms. pure HCl
= 1 cc

6/6/57

oxalic acid in acidimetry + alkalimetry

$H_2C_2O_4 \cdot 2H_2O$ ~~2H-O~~ ~~vonic~~



white crystals

$$1\ N\ Soln. = \frac{H_2C_2O_4}{2}$$

$$= \frac{126,05}{2} = 63\ gm./l$$

$\rightarrow 1\ N$

Making Ltr. Std Solns of Bases.

Usually quit weigh approx amount rapidly (as they take on H_2O)

NaOH 40 gm./l $\rightarrow$ 1 N

KOH 56 gm./l $\rightarrow$ 1 N

NaOH, contain Na_2CO_3

& KOH

& they give elaborate methods for getting rid of it & excluding the carbonate

In fact, some people prefer to use $Ba(OH)_2$ because the carbonate is insoluble. ~~the carbonate~~

But for most work it could be taken

Oxidation & Reduction Vol. Technique

1. must know equ. (same as for oxidimetry + alkalimetry)

2. must have primary std.

3. must know how stable colors are.

$Na_2S_2O_3$

↳ used in literally a thousand reactions where the final step is always the titration of Iodine

$$2Na_2S_2O_3 + I_2 \rightarrow \underset{\text{Sodium tetrathionate}}{Na_2S_4O_6} + 2NaI$$

colorless → colorless

$I_2 = Na_2S_2O_3$ or $Na_2S_2O_3 \cdot 5H_2O$

I_2 → N/6

$Na_2S_2O_3$ → 24.8 gm/l → 1N

→ 4.8 gm/l → 0.1 N

Starch + I_2 → blue color

Problems

p. 81 # 151

p. 82 # 154

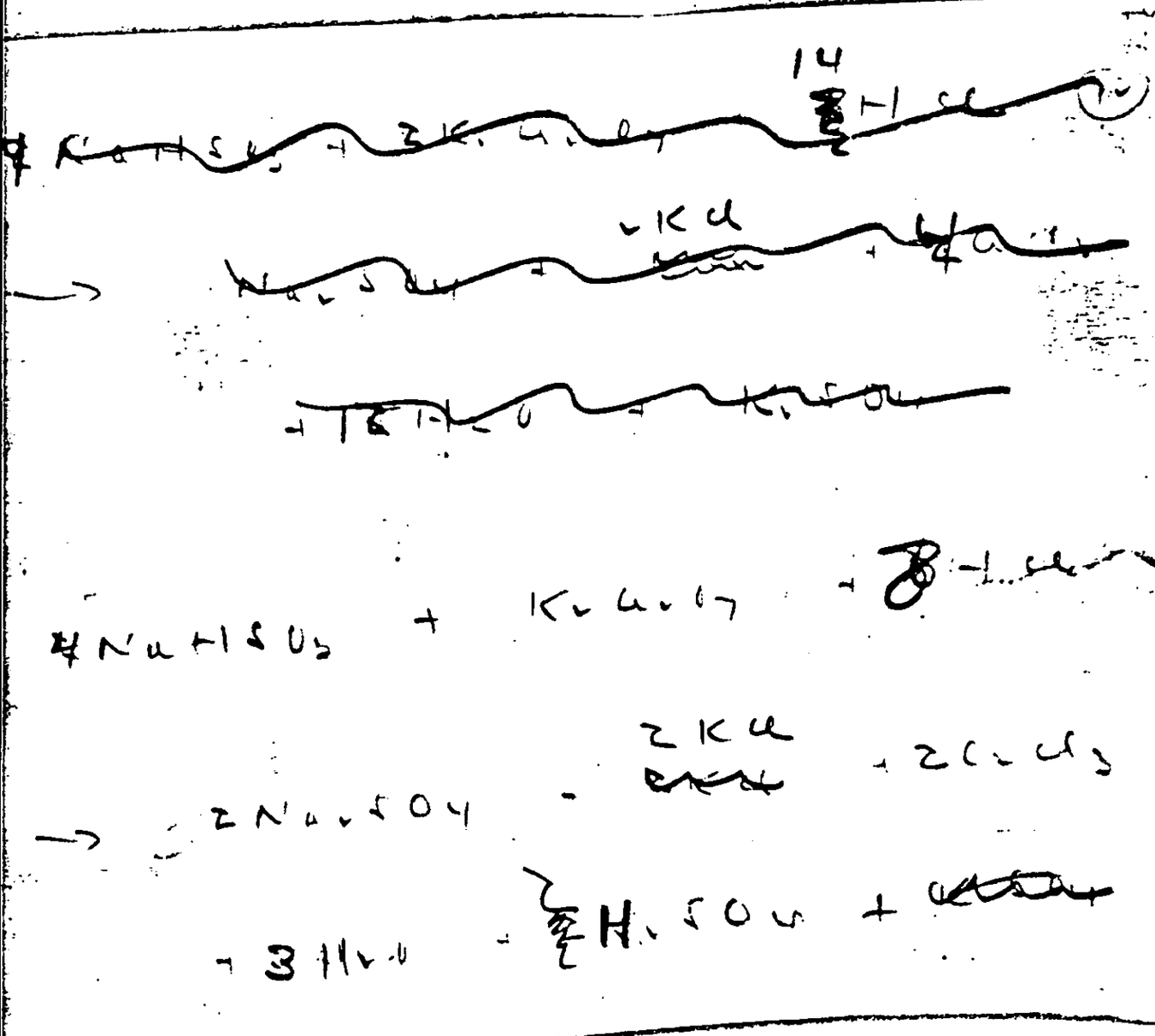
p. 83 # 162

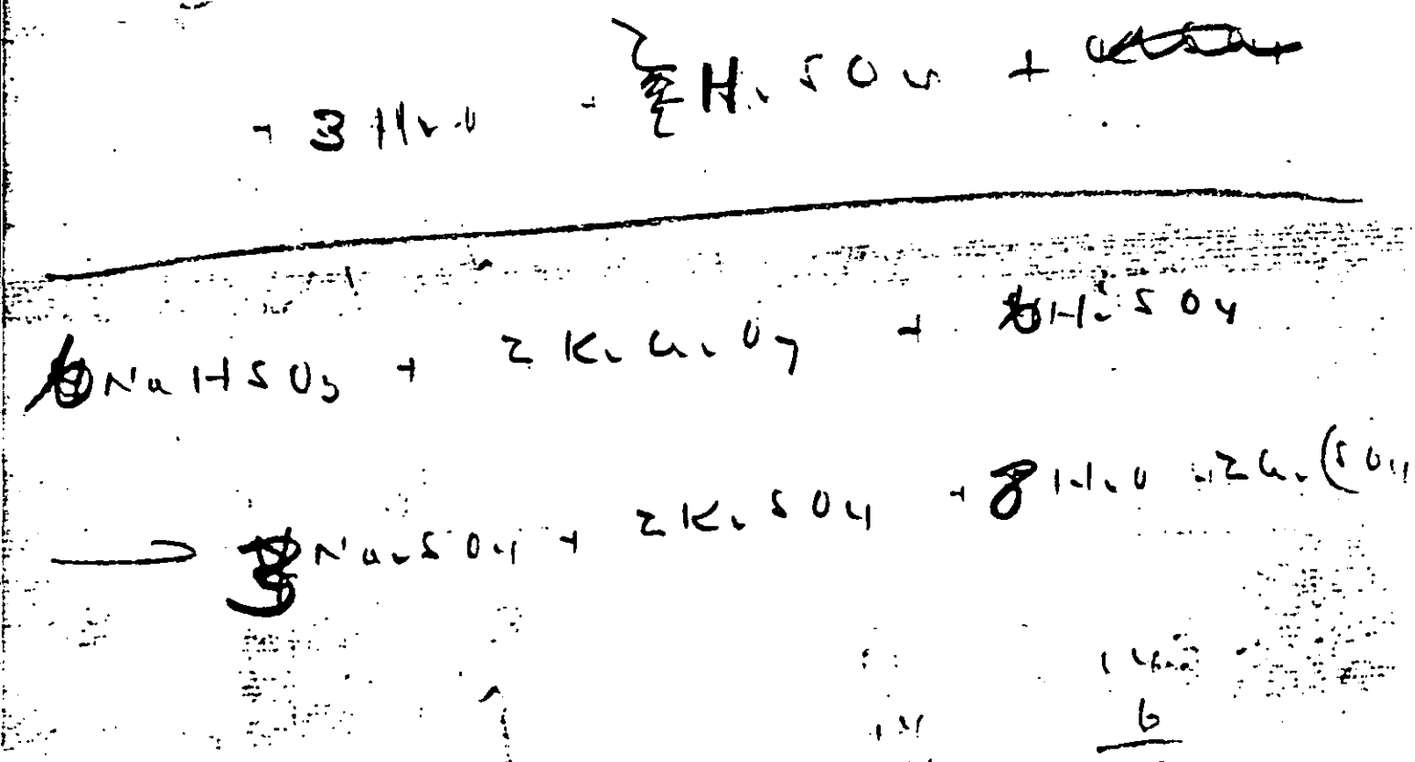
p. 83 # 164

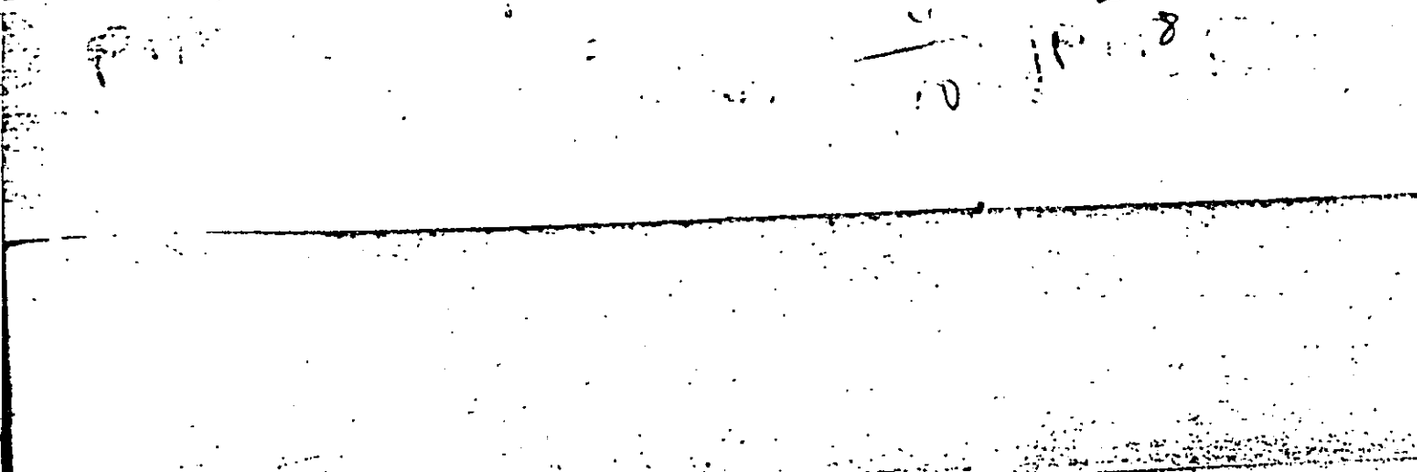
$$3NaHSO_3 + 2K_2Cr_2O_7 + 16HCl \rightarrow$$

$$3Na_2SO_4 + 3H_2SO_4 + 4KCl + 8H_2O$$
$$+ 4CrCl_3$$

6/6/50







#3

Received June 6, 1950

Joseph Gold
(Name of Contributor)

6123 Kindred St., Philadelphia Pa
(Address of Contributor)

To be returned. (Yes) (No)

Robert Master
(Name of Submitting Agency)

Description of Item 3 Manila Folder Market Photographs Brooklyn

File No. 65-4307-1-B-14

Photocopies

Nicotinic Acid

#3

6/6/50

ALLYL CYANIDE

$$2CuSO_4 + 4NaCN \longrightarrow 2CuCN + (CN)_2 + 2Na_2SO_4$$

$$CH_2{=}CHCH_2Br + CuCN \longrightarrow CH_2{=}CHCH_2CN + CuBr$$

Submitted by J. V. Supniewski and P. L. Salzberg.
Checked by Reuben G. Jones and H. T. Hanson, and Glenn F. Woodward.

1. Procedure

A). Preparation of Cuprous Cyanide.—(Note 1)—In an 8-l. round-bottomed flask fitted with a stopper carrying a mechanical stirrer, a separatory funnel, and a gas exit tube leading to a good hood (Note 2) are placed a solution of 650 g. (2.6 moles) of crystallized copper sulfate in 4 l. of water. The flask is surrounded by an oil bath and heated to about 80°. The stirrer is started and a solution of 255 g. (5.2 moles) of sodium cyanide (Note 3) in 650 cc. of water is added from the separatory funnel over a period of about one-half hour. Then the mixture is boiled until no more cyanogen gas is evolved. This requires about five to ten minutes. The voluminous cyanide, which begins to separate as a light tan precipitate as soon as any of the cyanide solution is added, is allowed to settle and the solution is decanted. The precipitate is filtered, then washed with water (1 l.) and finally with alcohol (500 cc.) and ether (300 cc.). After drying at 110° for about thirty-six hours, the product weighs 200–210 g. (85–90 per cent of the theoretical amount).

B). Allyl Cyanide.—In an 8-l. round-bottomed flask fitted with a condenser (Note 4) and a mechanical stirrer are placed 220 g. (1.83 moles) of allyl bromide (Note 5) and 170 g. (1.9 moles) of dry cuprous cyanide (Note 6). The mixture is heated on a water bath and the stirrer rotated slowly by hand until the reaction starts (about fifteen to thirty minutes). When the reaction once begins it becomes vigorous, and the heating bath must be replaced by a cooling mixture of ice and water in order to avoid loss of product through the condenser. After the vigorous reaction has subsided, the water bath is replaced, the mechanical stirrer is started and the mixture is heated until no more allyl bromide refluxes. This requires about one hour. The condenser is then set for distillation and the allyl cyanide is distilled from the flask by heating it in an oil bath with stirring (Notes 7 and 8). Upon redistillation, the allyl cyanide is pure and boils

BIOTIN AND PARA-AMINOBENZOIC ACID AS GROWTH FACTORS FOR THE ACETONE-BUTANOL ORGANISM, CLOSTRIDIUM ACETOBUTYLICUM

Sir:

Rubbo and Gillespie [Rubbo and Gillespie, *Nature*, 146, 838 (1940)] have recently reported that p-aminobenzoic acid (p. a. b.) is a growth factor for nine strains of *Cl. acetobutylicum*. They state that it is the only factor required by the organism. We are unable to confirm this conclusion.

In a previous paper [Oxford, Lampen and Peterson, *Biochem. J.*, 34, 1588 (1940)] we reported that *Cl. acetobutylicum* on a medium of glucose, asparagine and Speakman's salts requires the addition of biotin and of an unidentified factor from yeast. The basal was identical with that of Rubbo and Gillespie except that 0.11% of salts was added instead of the 1.2% which they used. Asparagine-ammonium sulfate or ammonium phosphate were also used as nitrogen sources.

In later experiments we have found that p. a. b. will replace the yeast factor. This activity together with the close agreement between the properties of the two make it evident that the active substance in our earlier preparations was either p. a. b. or some equivalent compound. However, growth does not occur on the addition of p. a. b. alone to the basal medium. If biotin is added also, growth is optimal. This result has been obtained with strain S9 from our collection and nos. 824 and 902 of the American Type Culture Collection. No. 902 is one of the strains used by Rubbo and Gillespie. All strains required both biotin and p. a. b. Table I illustrates the effect of the two factors on the S9 strain.

TABLE I

EFFECT OF BIOTIN AND P. A. B. ON *Cl. acetobutylicum* S9 (WISCONSIN COLLECTION)

Biotin (γ/cc.)	p. a. b. (γ/cc.)	Galvanometer reading
[illegible]	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00154	0.0005	[illegible]
.00154	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00154	[illegible]	[illegible]
.00154	0.2	[illegible]
[illegible]	[illegible]	[illegible]
.00001	[illegible]	[illegible]
.00002	[illegible]	[illegible]
.00005	[illegible]	[illegible]
.00010	[illegible]	[illegible]
.00020	[illegible]	[illegible]

Growth was determined by measuring the turbidity in an Evelyn photoelectric colorimeter. The biotin employed was the crystalline methyl ester obtained through the generous coöperation of Professor V. du Vigneaud.

Our only explanation of the discrepancy between our findings and those of Rubbo and Gillespie is that the natural constituents of their medium may have contained biotin. We have found that some grades of glucose contain appreciable quantities of this factor.

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WISCONSIN
J. O. LAMPEN
W. H. PETERSON

RECEIVED JULY 24, 1941

THE PREPARATION OF NICOTINIC ACID FROM PYRIDINE

Sir:

The recent report by Gilman and Spatz [Gilman and Spatz, THIS JOURNAL, 63, 1556 (1941)] on the preparation of 3-cyanoquinoline from 3-bromoquinoline and the hydrolysis of the cyano compound to the corresponding acid prompts the publication of a parallel synthesis in the pyridine series on which we have been working. Since 3-bromopyridine may be prepared by the direct bromination of pyridine [Englert and McElvain, *ibid.*, 51, 863 (1929); Wibaut, *et al.*, *Rec. trav. chim.*, 51, 381 (1932)], the synthesis now reported makes nicotinic acid readily available from pyridine. The following is the procedure by which 3-cyanopyridine (nicotinonitrile) was prepared. To 6.25 g. (1 mol) of 3-bromopyridine in a Claisen flask set for vacuum distillation was added 3.5 g. (1.5 mol) of cuprous cyanide ["Organic Syntheses," Coll. Vol. I, p. 38]. The mixture, which warmed spontaneously, was heated to 165–170° in an oil-bath for one hour. The resulting black viscous reaction product was then heated under about 20 mm. pressure with a smoky burner flame until no more volatile material came over. The nitrile that distilled over solidified in the receiver. After recrystallization from ligroin (b. p. 60–68°) the yield of product that melted at 49–50° [Fischer, *Ber.*, 15, 63 (1882)] amounted to 2.1 g. (50%).

3-Cyanopyridine is readily converted to nicotinic acid by hydrolysis. The following procedure was found to be satisfactory. A solution of 3.6 g. of 3-cyanopyridine and 4 g. of sodium hydroxide in 60 ml. of 70% alcohol was refluxed

...of three hours. The solvent was then removed by evaporation and the residue dissolved in 25 ml. of water. The aqueous solution after cooling to 0° was carefully neutralized with the calculated amount of hydrochloric acid. The precipitated picrolonic acid after recrystallization from water amounted to 3.5 g. (60%) and melted at 221–222°.

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M. Mohler
W. A. Cowdrey

Received July 24, 1941

THE CONCENTRATION OF "FOLIC ACID"

by

Using *Streptococcus lactis R* as a test organism we have obtained from a highly concentrated and probably nearly pure form an acid possessing interesting physiological properties.

Four tons of spinach have been extracted and carried through the first stages of concentration. A considerable portion of this material has been subjected to an extended process involving consecutively adsorptions on and elutions from charcoal, followed by successive precipitations with lead and silver salts and chromatographic adsorption on fuller's earth.

The material contains nitrogen, but neither sulphur nor phosphorus and has a molecular weight of about 300 as determined by diffusion of the acetone complex and possesses high physiological activity.

This acid, for which the name "folic acid" is suggested because of its physiological properties, occurs in a number of animal tissues of which liver and kidney are the richest sources. It is widespread in the biological kingdom. Mushrooms and yeast are good sources. It is especially abundant in green leaves of many plants, including grass. Because of this fact, and since we have obtained what appears to be a relatively pure chemical entity, we suggest the name *folic acid* (Latin, *folium*—leaf). Many common spontaneously fermented greens are nearly lacking in the substance.

The basal medium used for the microbiological test was the same as described in another publication [B. L. Snell and H. K. Mitchell, *Proc. Am. Soc. Exper. Biol. Med.*, 46, 1 (1941)] except that pyruvate, adenine, xanthine and uracil were added in amounts of 50 γ each per tube. In these latter substances increase the sensitivity of the test but are insensitive simply and collectively. Growth responses were determined by the thermoelectric turbidimeter of Williams, Hall and Williams [R. J. Williams, E. M. Hall and C. E. Williams, *J. Phys. Chem.*, 36, 2913 (1932)] and a growth curve may be illustrated as follows.

Folic acid (γ per tube)	Turbidity reading (arbitrary units)
0.0	0.7
0.005	11.0
0.010	29.8
0.0175	34.8
0.025	36.5
0.05	39.0

The concentrated substance stimulates the growth of *L. delbrückii* and *L. casei* with similar conditions and dosages.

Folic acid stimulates *L. casei* under the same conditions as the factor reported by Snell and Peterson [E. E. Snell and W. H. Peterson, *J. Bact.*, 39, 273 (1940)] and recently reported to be isolated by Stokstad [E. L. R. Stokstad, *J. Biol. Chem.*, 139, 875 (1941)]. A possible identity of the two substances is thus indicated, but chemical evidence shows dissimilarity since Stokstad reports a considerable phosphorus content in the factor he isolated while this element is absent from folic acid. Another marked difference lies in the degree of biological activity. Folic acid in the purest form obtained produces approximately half maximum growth in our microbiological test at a level of 0.00012 γ/ml., while this effect obtained by Stokstad under his testing conditions, is at about 0.011 γ/ml.

Indications have been obtained that the substance may have vitamin-like properties for animals. On a series of six rats on a control diet the average gain was 64 g. per 21 days. Five rats of the same litter gained an average of 71.5 g. (corrected for sex differences) when 50 γ of folic acid was given per rat per day. Two given 5 γ per day gained 68 g. The results of these tests on animals suggest bacterial production in the intestine.

Department of Chemistry
University of Texas
Austin, Texas

Esmond E. Snell
Roger J. Williams

Received June 23, 1941

AN ADDITION REACTION OF ALKALI-TREATED [illegible] INVOLVING A NEW SYNTHESIS OF [illegible]

We have recently reported (in press) conclusive evidence of a [illegible] toward alkali [illegible] such amino and thiocarbonic [illegible] and only [illegible] in [illegible] form [illegible]. At the same time, we

of perbromide bromine gave a 40% yield of 3,5-dibromopyridine but none of the 3-bromopyridine. A mixture of pyridine hydrobromide and this perbromide gave a 35% yield of 3-bromopyridine and a 10% yield of the dibromopyridine. The greatest yields of brominated pyridines were obtained when the lower perbromide was heated. In this case 36–38% yields of 3-bromopyridine and 30–36% yields of 3,5-dibromopyridine were obtained. The yield calculations were made on the basis of the bromine used in the preparation of the perbromides.

Experimental

Pyridine Hydrobromide Perbromide (47% Perbromide Bromine).—To a warm (60–65°) solution of 160 g. (1 mole) of pyridine hydrobromide in 240 g. of glacial acetic acid in a large beaker, a solution of 160 g. (1 mole) of bromine in 160 g. of acetic acid was added. The resulting solution was stirred thoroughly by hand and then allowed to cool. After two to three hours there was deposited a mass of large, orange-red, needle-shaped crystals. They were filtered off and dried in a desiccator. They were quite stable and when dry melted at 133–134°. The yield was 300–310 g. (95–97% based on the formation of $C_5H_5N \cdot HBr \cdot Br_2$). These crystals were analyzed for perbromide bromine by the method of Trowbridge and Diehl[7] and found to contain 47.0% of such bromine.

Pyridine Hydrobromide Perbromide (39.7% Perbromide Bromine).—This perbromide was prepared in exactly the same manner as the one described above except that 80 g. (0.5 mole) of bromine in 80 g. of acetic acid was added to the warm solution of 160 g. of pyridine hydrobromide in acetic acid. The crystals obtained melted at 101–103° and the yield averaged 205 g. Analysis showed 39.7% of perbromide bromine. There was no appreciable change in weight in either of these perbromides when they were allowed to stand in a vacuum desiccator over sulfuric acid for several days.

3-Bromopyridine and 3,5-Dibromopyridine.—These products were prepared in better yields from the lower perbromide. The perbromide containing 39.7% of bromine as perbromide as obtained in the preparation described above was mixed with the residue left by the evaporation of the acetic acid mother liquors. The weight of this mixture amounted to approximately the sum of the weights of pyridine hydrobromide and bromine (that is, 240 g.) used in the preparation of the perbromide. This solid mixture was heated in a round-bottomed flask under a reflux condenser in a sodium nitrate–potassium nitrate bath that was maintained at 230–250°. The solid melted at about 100° and as the liquid reached the bath temperature there was a vigorous evolution of hydrogen bromide. The evolution of hydrogen bromide gradually subsided and at the end of six to eight hours had practically ceased. During the reaction there was considerable condensation of crystals of 3,5-dibromopyridine on the cooler parts of the flask and in the reflux condenser. When the evolution of hydrogen bromide had ceased, the reaction mixture was steam distilled until no more crystals of 3,5-dibromopyridine appeared in the condenser. The distillate consisted of an acid solution and suspension of 3,5-dibromopyridine which was completely precipitated out by the addition of alkali. The precipitate was filtered off and recrystallized from alcohol. The yield was 18–23 g. of a product that melted at 110–111°. The residue left in the flask after the removal of the 3,5-dibromopyridine by steam distillation was made strongly alkaline with sodium hydroxide and again steam distilled. The distillate consisted of water, pyridine and 3-bromopyridine and as it first came over was clear, but as the proportion of water increased it became turbid and when about 250 cc. of distillate had been collected, a layer of 3-bromopyridine and some pyridine was present in the receiver. This layer was

Diehl[1] were unable to obtain a definite compound from bromine and pyridine in aqueous solution but in chloroform solution they obtained a compound which appeared to have the formula $C_5H_5N \cdot Br_4$. On standing this tetrabromide lost bromine and passed into a compound which analysis showed to have the formula $C_5H_5N \cdot Br_3$. Barthe[2] obtained from pyridine and bromine a perbromide to which he assigned the formula $C_5H_5N \cdot Br$. Trowbridge and Diehl also prepared perbromides of salts of pyridine. By passing bromine into an aqueous solution of pyridine hydrobromide they obtained two perbromides, one of which contained 41.95% of bromine and the other 83.66% of bromine that was present as perbromide bromine. The latter compound melted at 93° and the formula $C_5H_5N \cdot HBr \cdot Br$ was assigned to it. The perbromide containing 41.95% of perbromide bromine was assumed to be a mixture of $C_5H_5N \cdot HBr \cdot Br_2$ and $C_5H_5N \cdot HBr \cdot Br$. These investigators also prepared a perbromide in aqueous solution to which they assigned the formula $C_5H_5N \cdot HBr \cdot Br_2 \cdot H_2O$. It melted at 118–120° and contained 67.96% of perbromide bromine.

In the work which is reported here it was found that glacial acetic acid was a much better solvent than water for the preparation of these perbromides because both reactants (bromine and pyridine hydrobromide) were quite soluble in this medium and the perbromides which were formed, while very soluble in warm acetic acid, were quite insoluble in the cold acid. From one mole of bromine and one mole of pyridine hydrobromide in acetic acid solution there was obtained a perbromide that melted at 132–134°. The yield was 95–97% of the theoretical based on the formation of $C_5H_5N \cdot HBr \cdot Br_2$. While this formula requires 50% perbromide bromine content, there was found only 47% of perbromide bromine in the product that melted at 132–134°.

One mole of pyridine hydrobromide and one-half mole of bromine in glacial acetic acid solution gave a perbromide that melted at 101–103° and had 39.7% of perbromide bromine. The perbromide bromine in the compound of the formula $C_5H_5N \cdot HBr \cdot Br$ amounts to 33.3%. The authors are not able as yet to assign satisfactory formulas to these perbromides but it is hoped that further work will throw some light on this subject.

An attempt was made to use pyridine hydrochloride instead of pyridine hydrobromide for the preparation of these perbromides but it was found that the yields from the hydrochloride were considerably lower than those from the hydrobromide and that the perbromides of pyridine hydrochloride were very deliquescent and quite difficult to handle.

When these perbromides were heated at 230–250° under a reflux condenser, there was a vigorous evolution of hydrogen bromide with the formation of 3-bromo- and 3,5-dibromopyridine. The perbromide containing 47%

[1] Trowbridge and Diehl, THIS JOURNAL, 19, 658 (1897).

[2] Barthe, *Compt. rend.*, 145, 75 (1907).

separated, dried with solid sodium hydroxide and fractionated. The fraction that boiled at 160–175° amounted to 29–31 g. On redistillation practically all of this fraction boiled at 168–173°. The yield of the dibromopyridine was 30–36% of the theoretical and that of the 3-bromopyridine 36–38% of the theoretical based on the bromine used in the preparation of the perbromide.

The separation of 3,5-dibromopyridine from 3-bromopyridine by steam distillation of the former from acid solution was originally used by Ciamician and Silber[3] and is fairly satisfactory but not complete. There appears to be some of the di-substitution product left with the monobromopyridine even after prolonged steam distillation, and in the final distillation of the latter compound a small amount of the dibromopyridine usually crystallizes in the condenser.

When the perbromide of higher bromine content was heated under similar conditions, a 40% yield of the dibromopyridine was obtained but none of the 3-bromopyridine was found. It was thought that dilution of this higher perbromide with pyridine hydrobromide might increase the yield of the mono-substituted product but several runs in which 2 moles of pyridine hydrobromide was mixed with 1 mole of the higher perbromide gave an average of 10% yield of 3-bromopyridine and 30% yield of the 3,5-dibromopyridine.

Summary

A convenient method of brominating pyridine to 3-bromopyridine and 3,5-dibromopyridine has been described. It consists of the preparation of a perbromide of pyridine hydrobromide in glacial acetic acid solution and the transformation of this perbromide by heat into the bromopyridines.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

SYNTHETIC GLYCERIDES. I. PREPARATION AND MELTING POINTS OF GLYCERIDES OF KNOWN CONSTITUTION[1]

BY H. P. AVERILL, J. N. ROCHE AND C. G. KING

RECEIVED OCTOBER 23, 1928 PUBLISHED MARCH 6, 1929

The isolation of pure triglycerides from natural fats and oils is an uncertain and laborious process because of the difficulty of complete separation. Even when pure triglycerides have apparently been obtained satisfactory evidence is not available to indicate which of the possible isomers has been found. It was thought that progress could best be made through the synthesis of glycerides of known constitution and the study of their chemical and physical properties. Data thus obtained will be valuable in the study of the components of naturally occurring fats and oils.

It seemed probable that definite relationships might be found between certain physical properties of the fats and their molecular structure if sufficient data were available to warrant conclusions. The three sets of isomers (only one having fatty acids) prepared by Fischer[2] indicated that

[1] This paper is based upon a part of the theses submitted by H. P. Averill and J. N. Roche to the Graduate School, University of Pittsburgh, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] E. Fischer, *Ber.*, **53**, 1621 (1920).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE BROMINATION OF PYRIDINE[1]

BY S. MARY ELIZABETH ENGLERT AND S. M. MCELVAIN

RECEIVED OCTOBER 22, 1928 PUBLISHED MARCH 6, 1929

The preparation of 3-bromopyridine and 3,5-dibromopyridine by the direct bromination of pyridine has long been known as a rather difficult reaction to carry out. Nevertheless, it appears to be the simplest method available for the preparation of these particular bromopyridines in quantity. Hofmann[2] was able to prepare 3,5-dibromopyridine by heating pyridine dibromide, $C_5H_5N \cdot Br_2$, in a sealed tube for one hour at 200°. He obtained the same product by heating pyridine hydrochloride and bromine together in a sealed tube. In neither reaction did he report the formation of 3-bromopyridine. Later, Ciamician and Silber[3] prepared 3-bromopyridine along with 3,5-dibromopyridine by heating pyridine hydrochloride and bromine in a sealed tube as Hofmann had done. They, however, heated their mixture for a longer time (twenty-four hours) and at a higher temperature (210–220°). Their combined yield of the mono- and dibromopyridines was only 21% of the theoretical. Blau[4] reported an improvement over the earlier sealed-tube methods, which consisted essentially of passing a mixture of bromine and carbon dioxide through molten pyridine hydrochloride. By this procedure the combined yield of the mono- and dibromopyridines was 42% of the theoretical.

This communication reports what seems to be a distinct improvement over all of the older methods of bromination of pyridine. The procedure consists of heating a perbromide of pyridine hydrobromide at 230–250° under ordinary pressure until the evolution of hydrogen bromide ceases.

There appears to be considerable variation in the composition of the perbromides of pyridine and pyridine salts as reported in the literature. Anderson[5] and Hofmann[2] treated pyridine and pyridine hydrochloride in aqueous solution with bromine and obtained crystalline precipitates which showed fair stability and to which they assigned the formula $C_5H_5N \cdot Br_2$. Grimaux[6] treated pure pyridine with bromine and obtained a compound that crystallized in thin, red plates and melted at 126°. To this compound he assigned the formula $(C_5H_5N \cdot Br_2)_7HBr$. Trowbridge and

[1] A portion of the thesis submitted by S. Mary Elizabeth Englert to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Master of Science.

[2] Hofmann, *Ber.*, 12, 988 (1879).

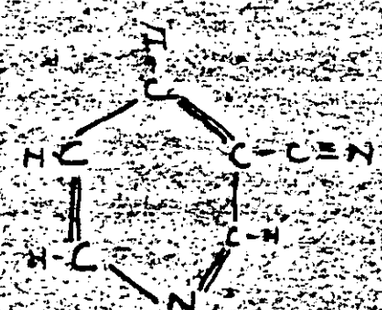
[3] Ciamician and Silber, *Ber.*, 18, 722 (1885).

[4] Blau, *Monatsh.*, 10, 372 (1889).

[5] Anderson, *Ann.*, 105, 341 (1858).

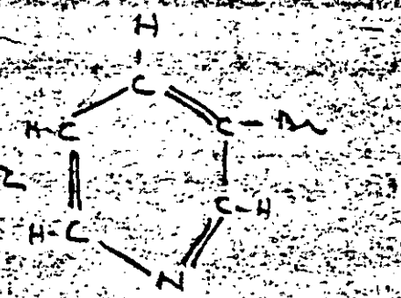
[6] Grimaux, *Compt. rend.*, 96, 85 (1883).

Exp 2



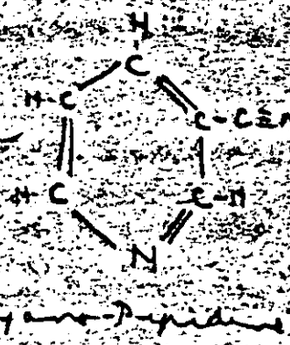
3-Cyano-Pyridine

1. Reaction



3-Bromo-Pyridine

+ $Cu_2(C{\equiv}N)_2$ Cuprous cyanide



3-Cyano-Pyridine + Cu_2Br_2

2. Reactants

3-Bromo-Pyridine

Cuprous cyanide

3. Reagents

None

4. Yield

50%

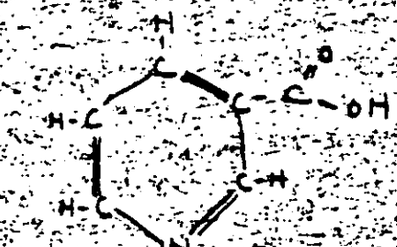
5. Unit operations

$A_2 - B_2 - C_2 - D_1 - H_1 - J_3 - L_1 - N_1 - P_4$

6. Solvents

Petroleum ether

Exp 3

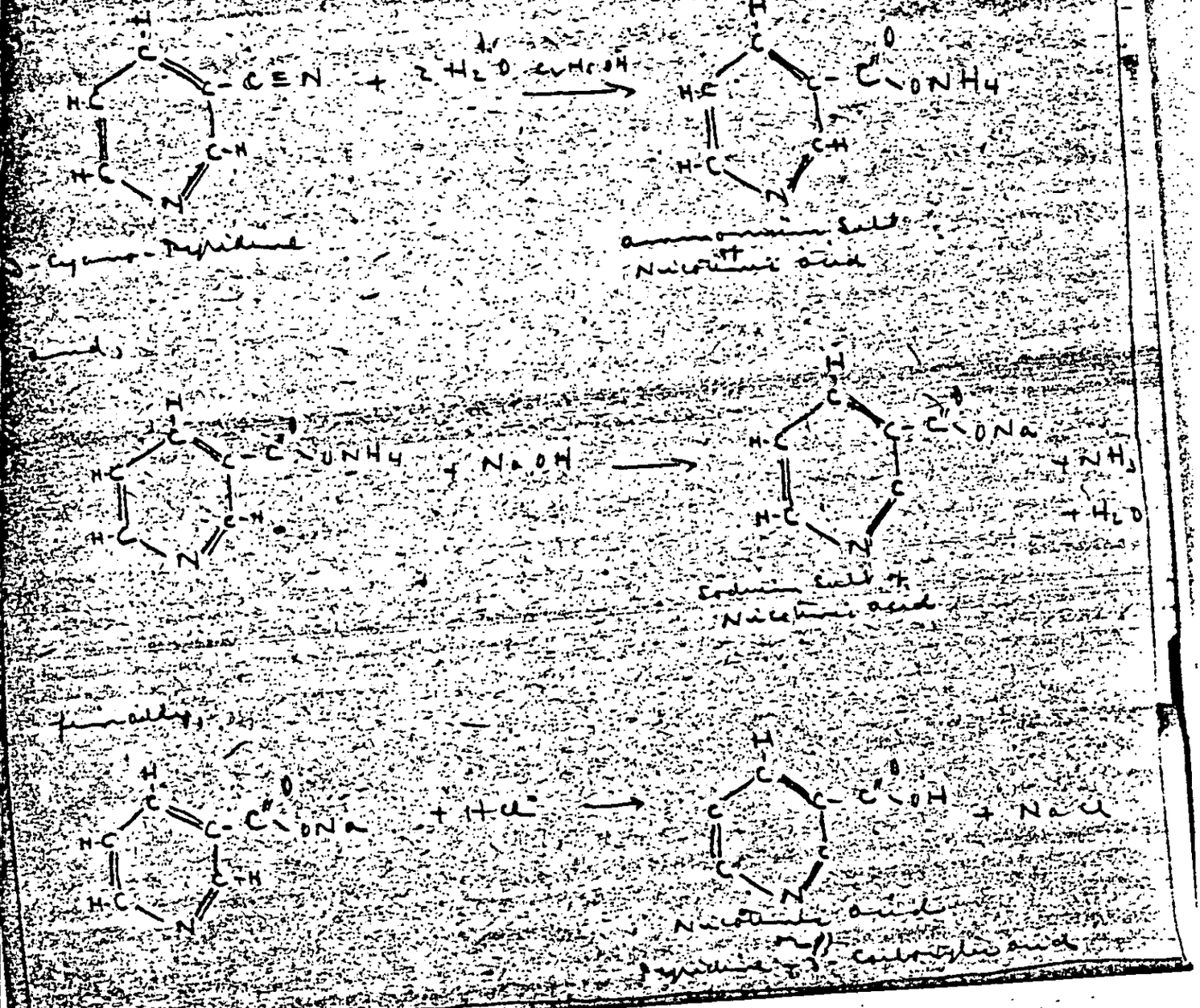


Nicotinic acid

or

Pyridine-3-carboxylic acid

Reaction



3-Cyano-Pyridine

Ammonium salt of Nicotinic acid

Sodium salt of Nicotinic acid

+ NH_3

+ H_2O

Nicotinic acid

Nicotinic acid

Ex 103 (cont'd)

2. Reactants

3-Cyano | Pyridine
Water |

3. Reactants

Sodium Hydroxide
Hydrochloric acid

Yield

90%

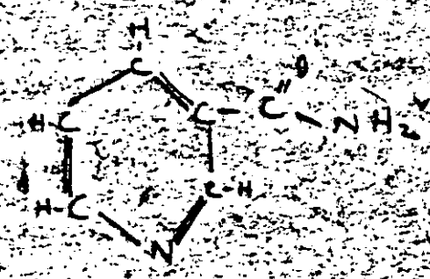
5. Unit operations

$A_2 - B_2 - C_2 - D_1 - W_1 - W_3 - L_1 - N_1 - P_4$

6. Solvents

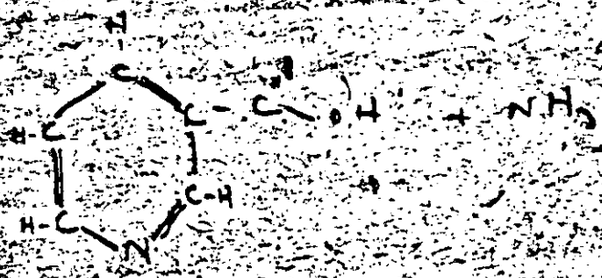
None

Exp 4

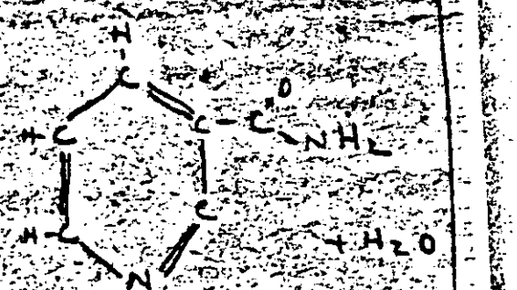


Nicotinamide
or
Pyridine-3-carboxylic acid-amide

1. Reaction



Nicotinic acid
or
Pyridine-3-carboxylic acid



Nikotinamide
or
Pyridine-3-carboxylic acid-amide

2. Reactants

Pyridine-3-carboxylic acid (Nicotinic acid)

ammonia (gas)

3. Reagents

None

4. Yield

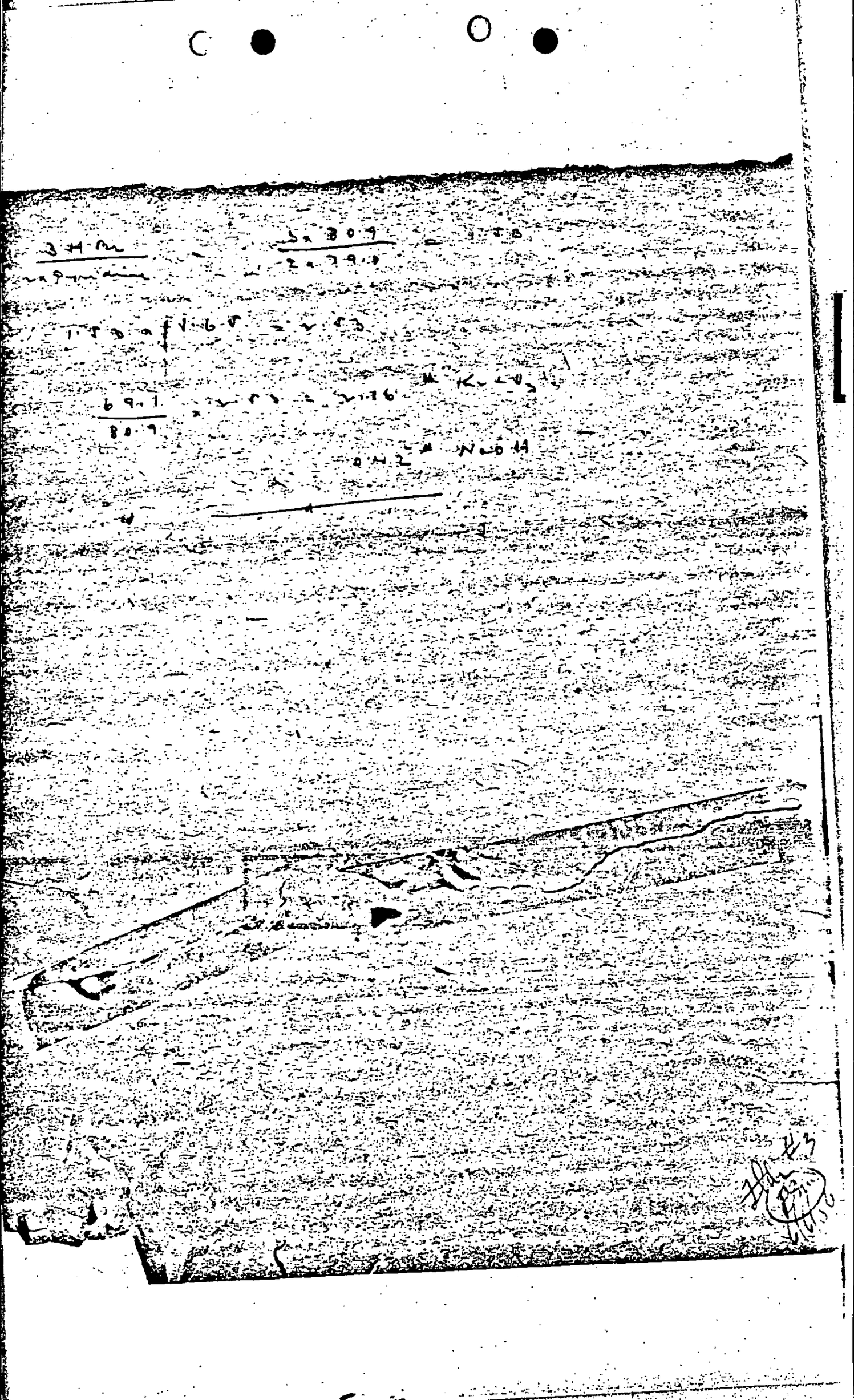
75 %

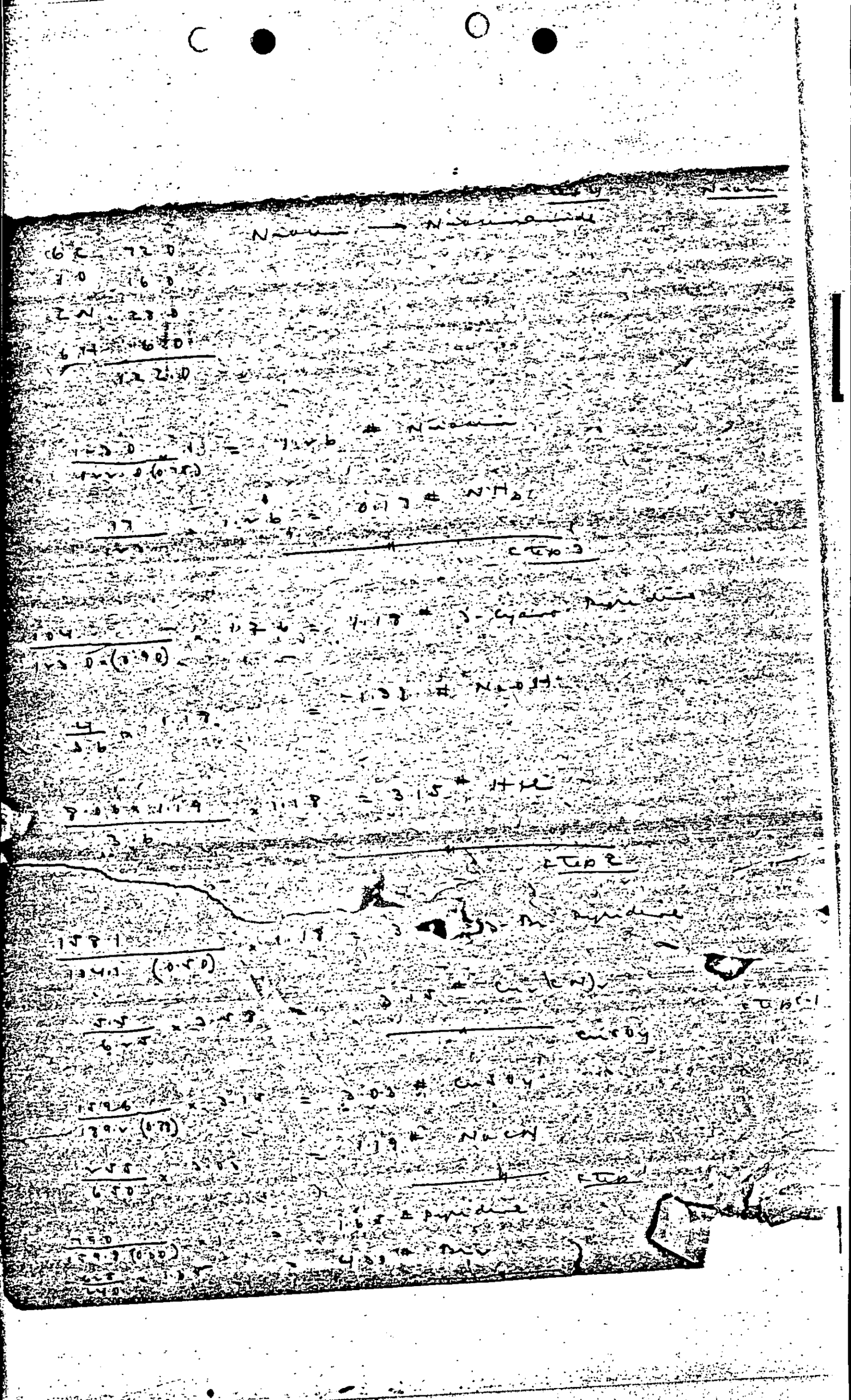
5. Reaction apparatus

$A_3 - B_1 - C_{III} - D_1 - I_1 - J_4 - L_1 - N_1 - P_4$

6. Educts

None





Group C-1

Group 2

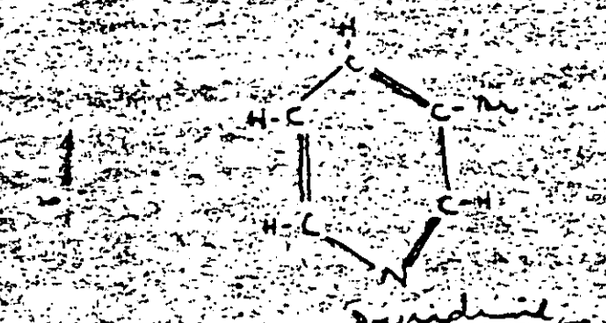
Group 3

Group 4

materials cost

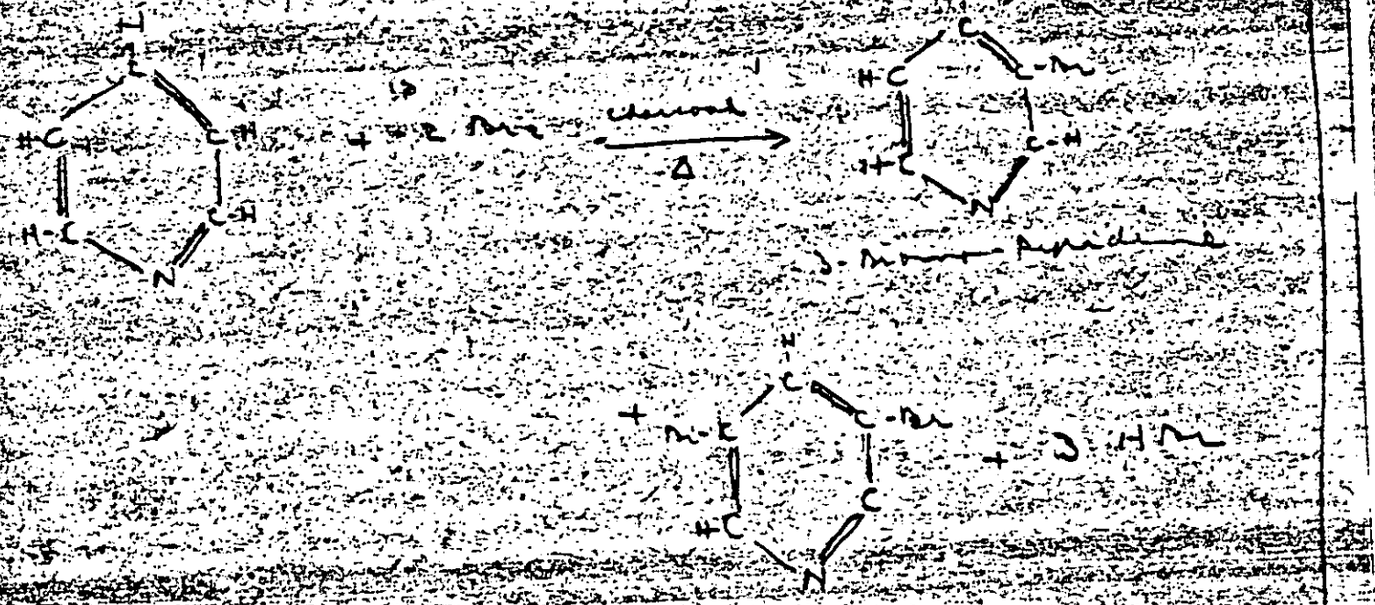
pyridine	1.65
Br	4.30
[illegible]	0.03
K_2CO_3	2.16
NaOH	1.73
$CuSO_4 \cdot 5H_2O$	8.93
NaCN	1.19
HCl	0.15
NH_3 (aq)	0.17

Exp 1



3-Bromo-Pyridine

Reaction



3,5-Dibromo-Pyridine

2. Reactants
Pyridine
Bromine

3. Reagent
Concentrated Sulfuric Acid

4. Product
3,5-Dibromopyridine

5. Equations
$A_2 + B_1 \rightarrow C_2 + B_1 + H_2 + J_4 + P_2$

6. Solvent
Sodium Hydroxide (9 to 10)

Copper sulfate

Step C-1

1. $Cu_2(C\equiv N)_2$

Cuprous cyanide

2. Reaction

$2\,CuSO_4 + 4\,NaC\equiv N \longrightarrow Cu_2(C\equiv N)_2 + (CN)_2 + 2Na_2SO_4$

Cuprous cyanide

3. Reactants

Copper sulfate

Sodium cyanide

4. Reagents

Nil

5. Yield

82.7 %

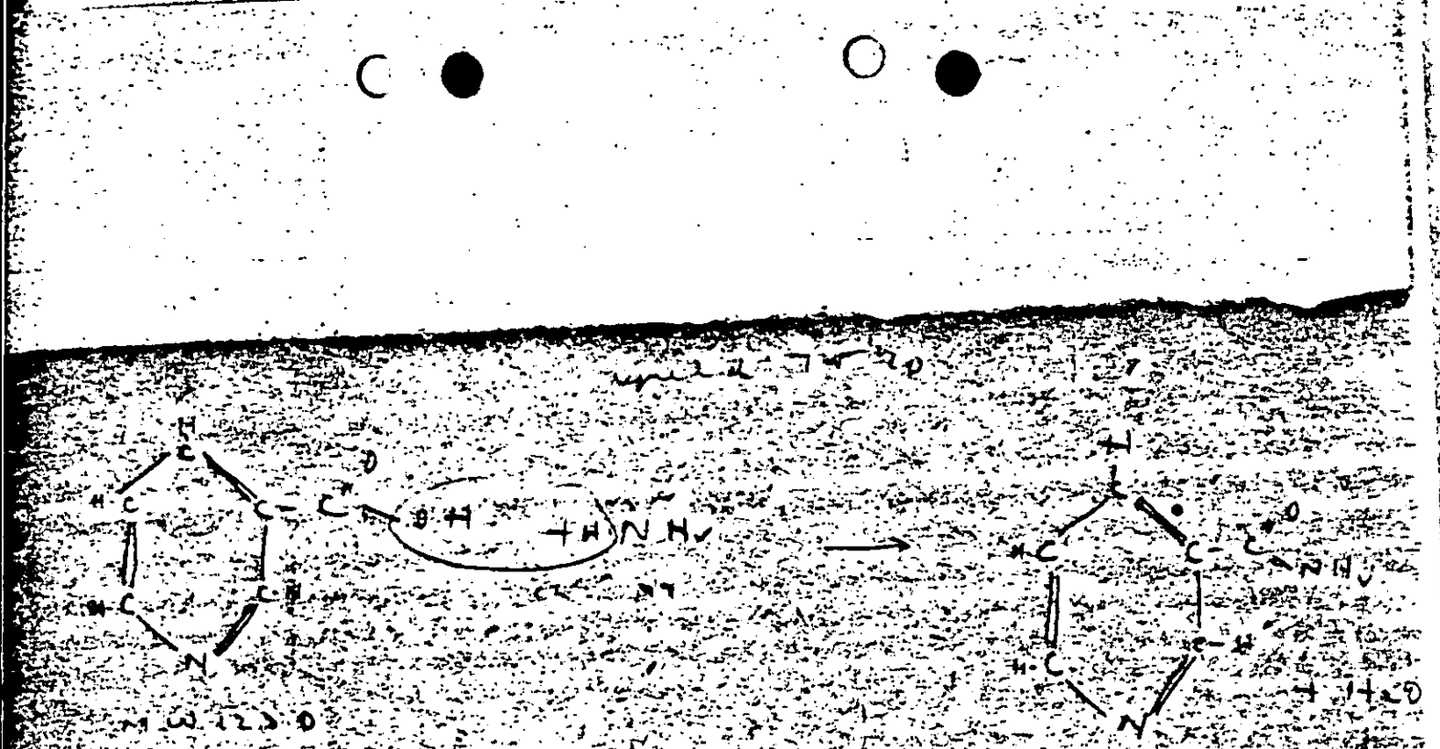
6. Unit reactions

$A_7 - B_2 - C_5 - I_3 - J_4 - L_1 - N_1 - P_7$

7. Solvents

Ethyl alcohol (95%)

Ethyl Ether



Filter the Nicotinic acid crystals

Wash the crystals once with 4 cc of water at

5°C

Dissolve the Nicotinic acid in 40 cc of hot

H2O

Evaporate the solution to one

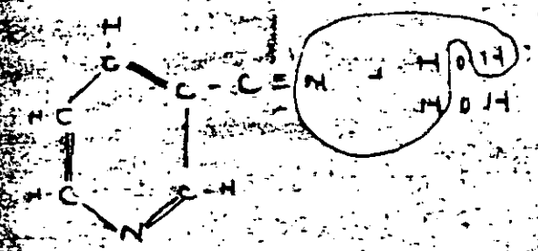
Cool the solution to 5°C The Nicotinic acid

crystals precipitate

Filter the Nicotinic acid crystals

Dry the crystals

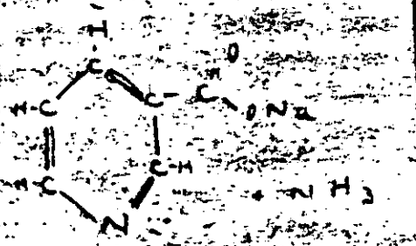
Yield 90%



3-cyano-pyridine

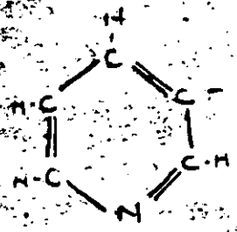
M.W. 104.0

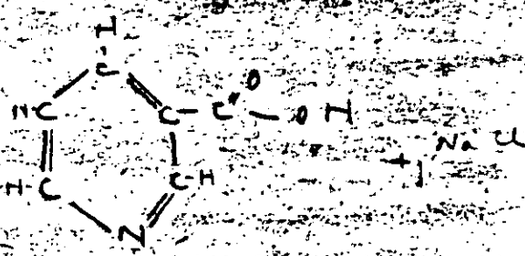
m.p. 49°-50°C



Sodium salt of Nicotinic acid

and,





Nicotinic acid

or

pyridine-3-carboxylic acid

M.W. 123.0

m.p. 231°-232°C

To dissolve { 2.6 gms of 3-cyano-pyridine and 4 gms of NaOH } in 40 cc of 70% ethanol

2. Reflux the soln (at temp 90°C (b= 194°F)) for 5 hrs

3. Evaporate the soln to dryness

4. Dissolve the residue in 25 cc of H_2O.

5. Cool the soln to 0°C

6. Exactly neutralize the soln with 30 cc of 6.7 N HCl; Nicotinic acid crystals will begin to

Yield 87 %

$$2\,CuSO_4 + 4\,NaCN \longrightarrow Cu_2(C{\equiv}N)_2 + (CN)_2 + 2\,Na_2SO_4$$

m.w. 159.6 — 49.0 — 179.2

Dissolve { 650 grams of $CuSO_4 \cdot 5H_2O$; 4000 cc of H_2O }

Heat the solution to 80°C (176°F),

add { 245 grams of NaCN dissolved in 650 cc of H_2O } under agitation,

and boil a ½ hr period.

Boil the solution for 10 minutes and cool to room temperature.

Cool the solution to 25°C.

Allow the CuCN crystals to settle and decant the supernatant liquid.

Filter the crystals.

Wash the crystals with 1000 cc (total) of water.

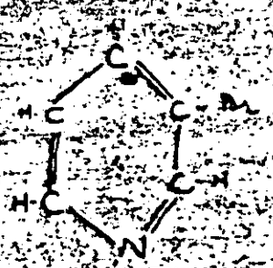
Wash the crystals with 500 cc (total) of alcohol.

Wash the crystals with 300 cc (total) of ether.

Dry the crystals at 110°C for 36 hrs. (25)

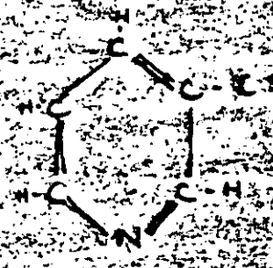
250°F

Yield 50%



3-Bromo-Pyridine
MW 158.1
1.5 gm
(.01 mol)

+ $Cu_2(CN)_2$
cuprous cyanide
MW 139.2



3-cyano-Pyridine
MW 104.1
— P. 49-50°C

Reactants { To 6.25 gms of 3-Bromo-Pyridine add 5.5 gms of $Cu_2(CN)_2$

The mixture warms spontaneously - heat the mixture to 160°C (320°F) for 1 hour. A black, viscous reaction product results.

Distill the black reaction product at 440°C (752°F) and 20 mm Hg pressure. The more volatile cyano-pyridine molecules will distill over the more volatile

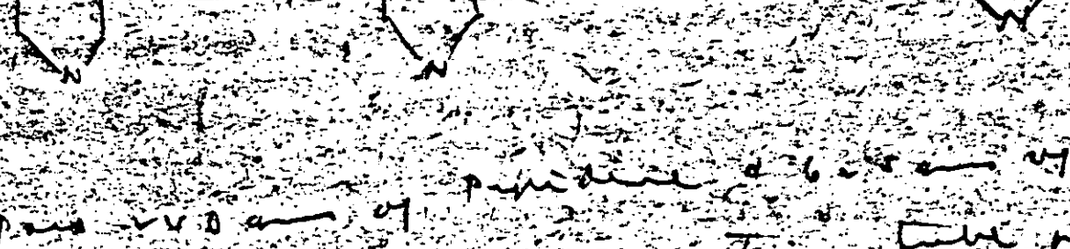
Dissolve the cyano-pyridine in 10 cc of petroleum ether.

Evaporate the solution to 4 cc.

Cool the solution to 5°C to obtain a crop of cyano-pyridine crystals

Filter the crystals

Dry the crystals



#4

Date Received June 6, 1950

Joseph Field
(Name of Contributor)

6823 Kinbrook St, Phila
(Address of Contributor)

Robert G. Houston
(Signature of Agent)

To Be Returned

Description: 1 manila folder marked Pantothenic Acid

File No. 65-ft-347-1B-14

grid 2 [illegible]

2,2-Dimethyl-3-hydroxypropionaldehyde

M.W. 102.1

Reactants
- 100 gm isobutraldehyde
- 114 gm 40% formaldehyde

and the mixture in an ice bath

add 160 gm K_2CO_3 at a rate such that the temperature of the reaction mixture does not exceed 20°C.

After all of the K_2CO_3 has been added, the stirring is continued for 1 hr. During this period the temperature is allowed to rise to 25°C. The product is a viscous liquid.

The viscous liquid is extracted with ether. The ether extract is dried over Na_2SO_4.

The ether is distilled off.

The residue is cooled to solidify.

The residue is distilled under a 15 mm vacuum and the portion boiling

at 75°-76°C and taken. The distillate crystallizes immediately

10. The crystals are dissolved in alcohol

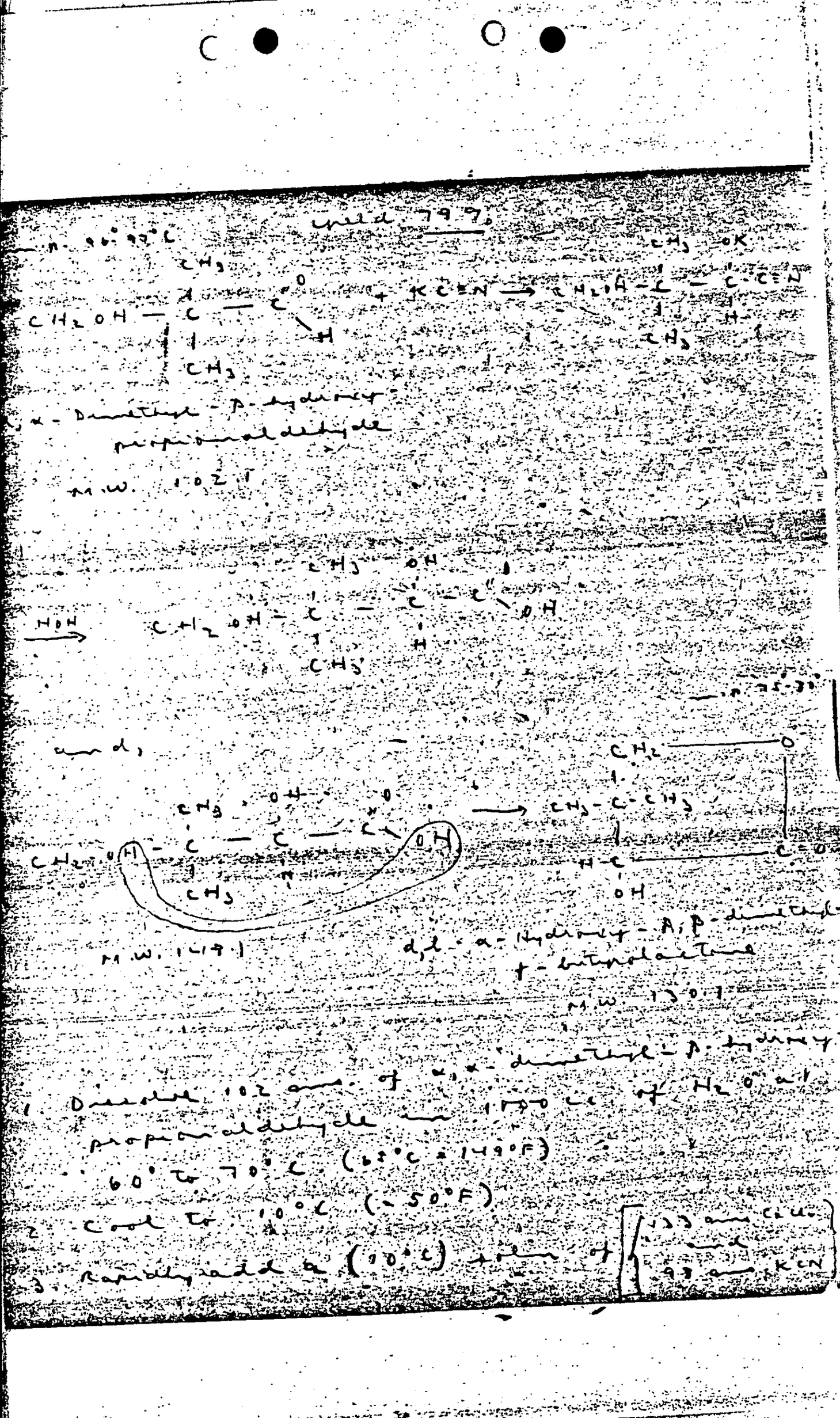
and the alcohol evaporated to ½ volume

11. The soln. is cooled → purified crystals

12. The crystals are filtered

13. The crystals are dried at 60°C (140°F)

under vacuum


m.p. 90-92°C
yield 79%
CH3
CH2OH — C — C
CH3
H
O
+ KC≡N
CH3
CH2OH — C — C — C≡N
CH3
H
OK
α-Dimethyl-β-hydroxy propionaldehyde
m.w. 102.1
HOH
CH3
CH2OH — C — C — C
CH3
H
O
OH
m.p. 75-77°
yield
CH2
O
CH3 — C — CH3
H — C
C = O
OH
d,l-α-Hydroxy-A,P-dimethyl-γ-butyrolactone
m.w. 130.1
1. Dissolve 102 gms. of α,α-dimethyl-β-hydroxy propionaldehyde in 1750 cc of H2O and
60° to 70°C (65°C = 149°F)
2. Cool to 10°C (~50°F)
3. Rapidly add a (10°C) [illegible] of [illegible] 130 gms CuSO4
95 gms KCN

4000 cc H_2O] and let stand for 12 hrs

at 25°C with occasional agitation.

This must be done in a CO_2-free atmosphere

4. Heat the soln. to 75°C (167°F)

5. add 150 gms of $Ca(OH)_2$

6. Filter off the $CaCO_3$

7. Evaporate the filtrate to a gum under vacuum. as much of the water as possible should be removed.

8. extract the residue with 1000 cc (total) of anhydrous acetone.

9. Filter out the insoluble material

10. Concentrate the acetone soln. to a viscous (syrup 120 cc) under vacuum

11. Take up the oil in 1000 cc of dry acetone

12. Evaporate the acetone

13. Distill (fractionate) the residue at 125-130°C and 13 mm. vacuum an oil is obtained which immediately solidifies to a glass in the receiver

14. Dissolve the lactone in say 5000 cc of cold (5°C) ethyl ether

15. add ethyl (5°C) petroleum ether till the

after the reaction is over, allow the mixture to stand overnight.

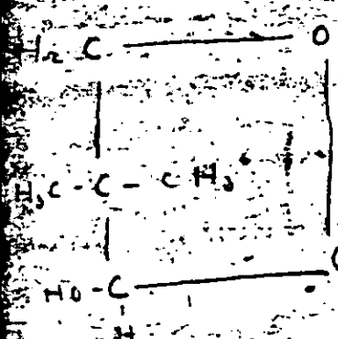
Next day, cluster of fine colorless needle crystals appear.

Filter the crystals.

Wash them with 2 to 3 portions of 50% petroleum ether.

Dry the crystals.

Lactol 3.1.70



dl-α-Hydroxy-β,β-dimethyl-γ-butyrolactone
M.W. 130.1

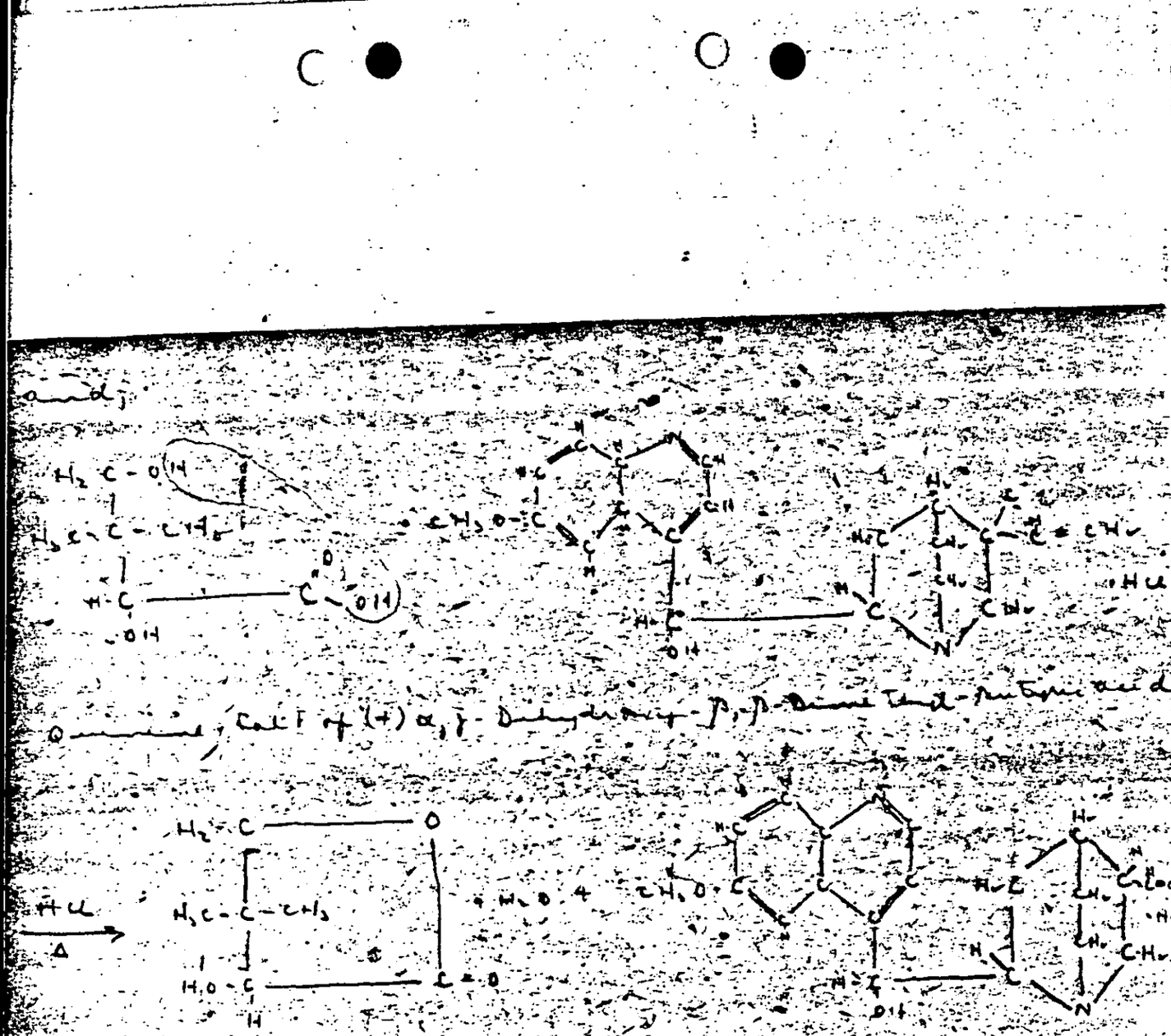
α,γ-Dihydroxy-β,β-dimethyl-butyric acid
M.W. 148.1

and

Quinine hydrochloride
M.W. 360.9

Quinine salt of (+) α,γ-Dihydroxy-β,β-dimethyl-butyric acid
(anhydrous solvate)

Quinine salt of (-) α,γ-Dihydroxy-β,β-dimethyl-butyric



Q-mucic, Calcd of (+) α,β- Dihydroxy-β,β-Dimethyl-Butyric acid

(-)α-Hydroxy-β,β-Dimethyl-γ-Butyrolactone

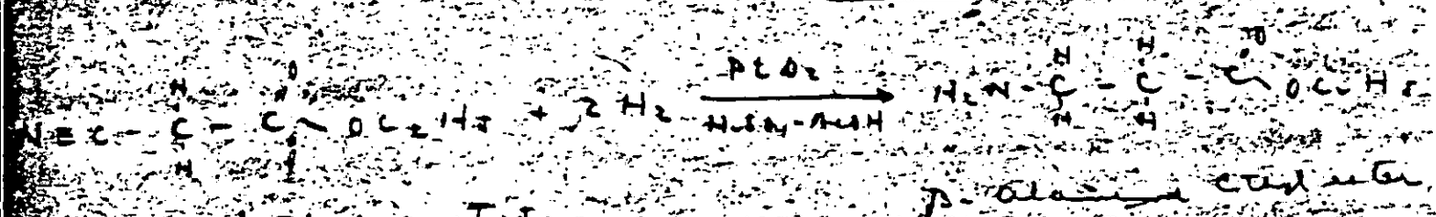
M.W. - 130.1

1. 27 gms of racemic lactone are dissolved in 85 cc of H-O
2. 46 cc of 3.372 N NaOH (773 gms = 46 cc) are added.
3. The solution is heated to 35°C (175°F)
4. The solution is cooled to 20°C (68°F)
5. The excess alkali (0.72 gms) is neutralized with 7.2 cc of 2 f N HCl (= 1 atom of H)
6. The solution is diluted to 400 cc and again heated to 35°

32 gms of guanine hydrochloride are added
to the hot soln with stirring. Separation
of the crystalline guanine salt of (+) α,ε-
diaminopimelic acid commences
after only a small part of the guanine salt
is added.
The soln and crystals are chilled to 0° C.
and kept at 0° C for 12 hrs
The crystals are filtered off
The crystals are washed twice with cold
water
The crystals are dried at 60° C. (yield 32 gms)
The mother liquors from 9 and 10 are
concentrated to abt 100 cc. a further
crystallization of the guanine (+) salt takes
place
The soln is cooled to 20° C and and
the crystals filtered
The added crystals are washed twice with
H₂O
The added crystals are dried at 60° C.
The two crops from 11 and 16 are
combined.
The combined crops are dissolved in
34 cc of 2.5 N HCl (= 17 cc of 38% HCl).

19. The soln is heated at 100°C for 20 mins
20. The soln is cooled to 20°C
21. The soln is continuously extracted for
11 hrs with ether
22. The ether soln is evaporated to dryness
23. 50 c.c. of 95% Ethanol + 5 c.c of Benzol
are added
24. The Ethanol-Benzol-H_2O azeotrope is
distilled off and the remainder of
the ethanol is also driven over to
leave a dry residue.
25. The residue is dissolved in a soln of
10 c.c of Benzol + 40 c.c of Petroleum Ether b.p. 40°C
26. The soln is evaporated to 20 c.c.
27. The soln is cooled to 10°C to yield a
crop of crystals
28. The crystals are filtered
29. The crystals are dried in air

Yield 74%



Cyano-ethyl acetate

M.W. 113

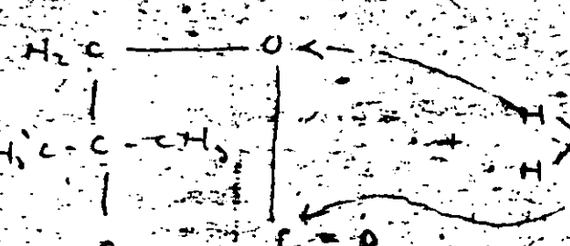
b.p. 208°C

Reactants { 30 gms cyano-ethyl acetate; 400 cc acetic acid (420 gms); 10 cc conc. H-SO4 (18.4 gms) }

1. Mix the reactants and add 3 gms of PtO_2 hydrogenating catalyst
2. Pass in H_2 under 40 atmospheres pressure and agitation at 22°C (72°F) for 1 hr. (The theoretical amount of H_2 is 10.6 gms)
3. The catalyst is filtered off
4. The acetic acid is distilled off under 12 mm vacuum
5. Add 75 gms of H_2O at 0°C and keep the solution at this temperature
6. Add strong caustic (aqua 40%) dropwise under cooling and with strong agitation until a pH of 8.0 is reached (it should require 14 cc of 50% caustic soda to reach pH 8.0)

8. Add 250 cm. of anhydrous K_2CO_3, mix
well (say 250 cm) pour a stiff
paste results
9. Wash the cake with 500 cc portions
of ether
10. To the combined ether washings add
anhydrous K_2CO_3 (say 100 gm) to dry
the ether soln.
11. Filter off the K_2CO_3
12. Distill off the ether under vacuum
and then distill the β-diamine ether
ether also under vacuum

Yield - 6.1.70

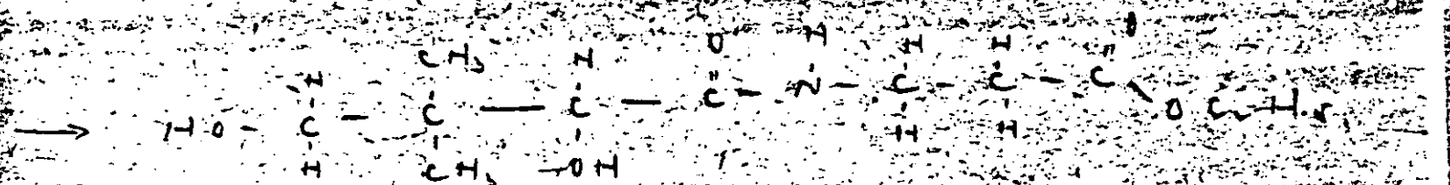


β-alanine ethyl ester

M.W. 117.1

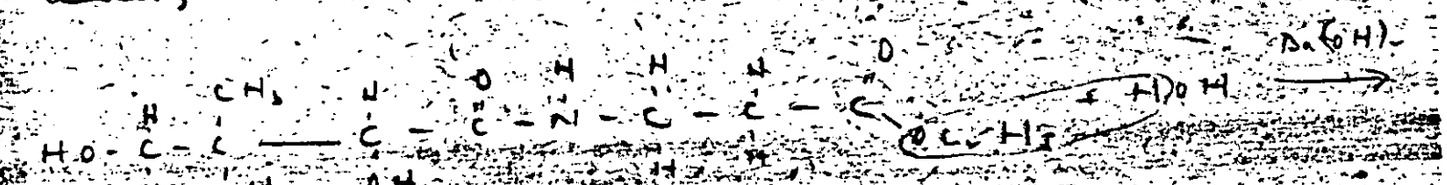
(-) α-Hydroxy-β,β-Dimethyl-γ-butyrolactone

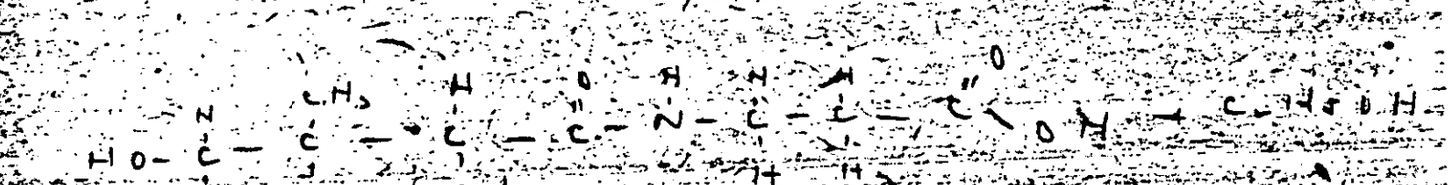
M.W. 130.1



(+) Pantothenic acid ethyl ester

and,





(+) Pantothenic acid.

M.W. 219.2

or

(+) - α, γ - Dihydroxy - β, β - Dimethyl - Butyryl - β - alanide

was prepared by condensing 3.75 gms. of (-) α - Hydroxy - β, β - Dimethyl γ - Butyrolactone with 7.5 gms. of β - alanine ethyl ester

2. Heat the mixture for 2 hrs at 71°C (150°F).
3. Cool the mixture to 25°C (77°F).
4. Add 300 cc of 0.45 N $Na(OH)_2$ ($2.5 gm $Na(OH)_2 \cdot 3H_2O$ made up to 300 cc).
5. React at 25°C for 2½ hrs.
6. Add 22.6 cc of 6N H_2SO_4 (= 3.35 cc of 94% H_2SO_4 made up to 22.6 cc) to ppt the $BaSO_4$.
7. Centrifuge out the $BaSO_4$.
8. Wash twice with 100 cc portions of H_2O.
9. Adjust the pH to 5.5 with pyridine.
10. Evaporate the soln to dryness in vacuum at 25°C to yield a colorless syrup.
11. Dry the syrup in a high vacuum over H_2SO_4.
12. Dissolve the syrup in 20 cc of MeOH.
13. Add 12.00 cc of acetone slowly with vigorous agitation.
14. Cool to 0°C and keep till the oil separates and partially crystallizes and the supernatant liquid is clear.
15. Filter at 0°C.
16. Dissolve the acetone insoluble material

in 20 cc of MeOH.

17. add 1200 cc of acetone slowly with vigorous agitation

18. cool to 0°C and stir till the precipitate

19. Filter at 0°C

20. Dissolve the acetone insoluble material in 20 cc of MeOH

21. add 1200 cc of acetone slowly with vigorous agitation

22. cool to 0°C and stir till the precipitate

23. Filter at 0°C

24. Combine the acetone-methanol liquors from "15", "19" and "23" and evaporate to dryness in vacuum at 25°C to yield a pale yellow oil

25. Dissolve the oil in 40 cc of H_2O

26. Neutralize to pH 7.5 with 0.9 N NaOH

27. Continuously extract the liquid with ether for 18 hrs. to remove a small amount of unchanged lactone

28. add 1 - 6N H_2SO_4 to ppt the Ba ion

29. Filter off the $BaSO_4$

30. Wash the cake twice with 40 cc portions of H_2O

33. The aqueous liquors from 29 and 30 are combined and pyridine is added to adjust the pH to 5.0.

34. The soln is evaporated to dryness under vacuum at 25°C. a pale yellow oil remains as product

35. The oil is dried under high vacuum over H_2SO_4.

36. The dry oil is extracted twice with 450 cc portions of acetone after vigorous agitation with the acetone.

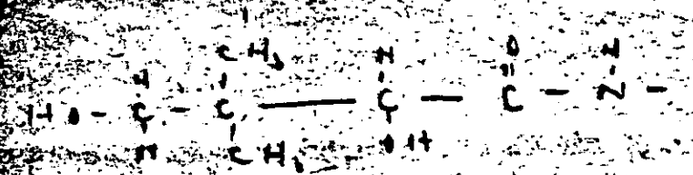
37. The combined extracts were cooled to 0°C and kept at this temperature till the supernatant liquid had cleared. a small amount of crystals of P. alanine formed

38. Filter off the P. alanine crystals.

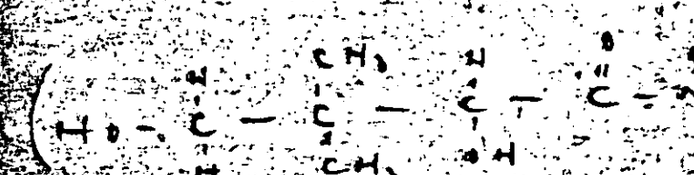
39. Evaporate the acetone soln to dryness in vacuum to yield a pale yellow ump.

40. Dry the ump in high vacuum at 40°C over H_2SO_4.

yield 82.7%



(+) Pantothenic acid
m.w. 219.2



(+) Ca Pantothenate m.w. 476.5

or

Ca salt of (+)-α,γ-Dihydroxy-β,β-Dimethyl-Butyryl-β-alanine

1. 3.5 gms. of (+) Pantothenic acid are dissolved in 20 cc. of H_2O
2. add 1.0 gms. $CaCO_3$ (~0.7 equiv.) under agitation.
3. Filter off the excess $CaCO_3$
4. Wash the cake twice with 5 cc portions of water.
5. Evaporate the combined filtrate and washings under vacuum to yield a hard colorless glass.
6. Dissolve the glass in ~15 cc of MeOH (until the minimum amount of MeOH) a small amount of insoluble material forms.
7. Filter off the insoluble material

8. add the MnO_4 soln. slowly with vigorous agitation to ~~and~~ 500 c.c. of acetone, a colorless microcrystalline powder forms.

9. Filter off the precipitate

10. Dry the crystals at 77°C (170°F) in vacuum

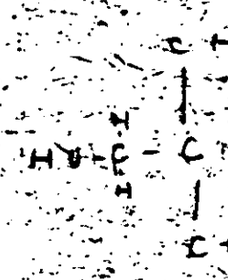
Isobutyraldehyde - Trade name 2-M

Prep by oxidation of isobutyl alcohol with
peroxide and

Isobutyl alcohol

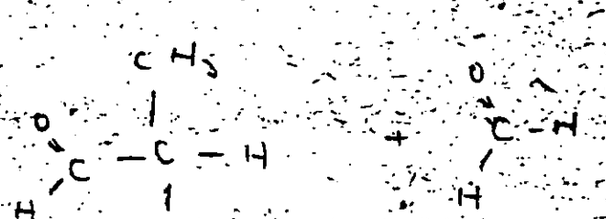
Made by fractional distillation of fusel
oil

Isobutyraldehyde



α, α - Dimethyl - β - Hydroxy - Propionaldehyde

1. Reaction



Isobutyraldehyde + Formaldehyde → α, α - Dimethyl - β - Hydroxy - Propionaldehyde

2. Reactants

Isobutyraldehyde
Formaldehyde (47.7% Formalin)

3. Reagents

K_2CO_3

4. Yield

76%

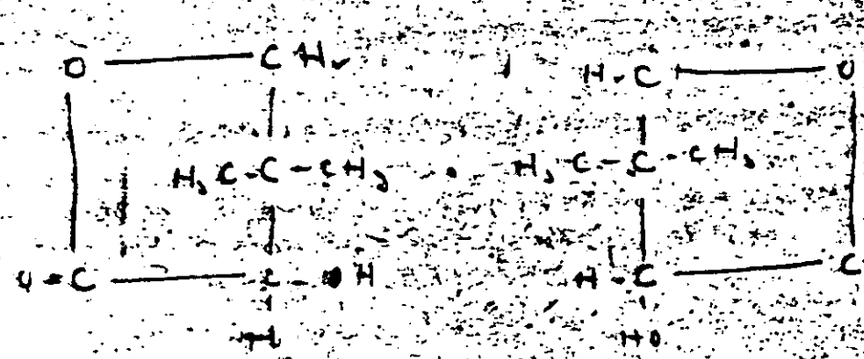
5. Unit operations

$A_5 - B_2 - C_5 - D_2 - E_1 - H_1 - I_1 - J_2 - L_1 - N_2 - P_2$

6. Solvents

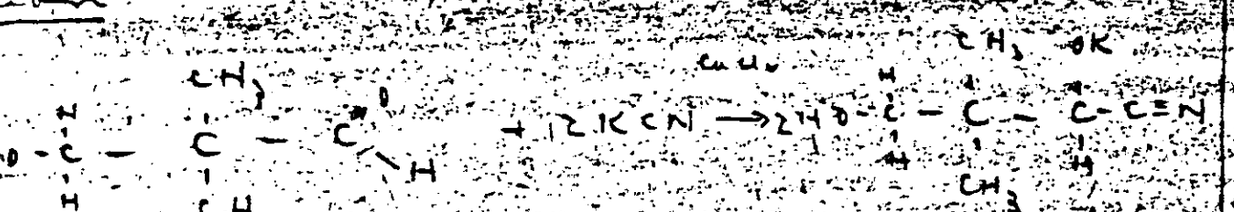
Ethyl Ether
Ethyl alcohol

Step 2



d, l - α - Hydroxy - β, β - Dimethyl - γ - Butyrolactone

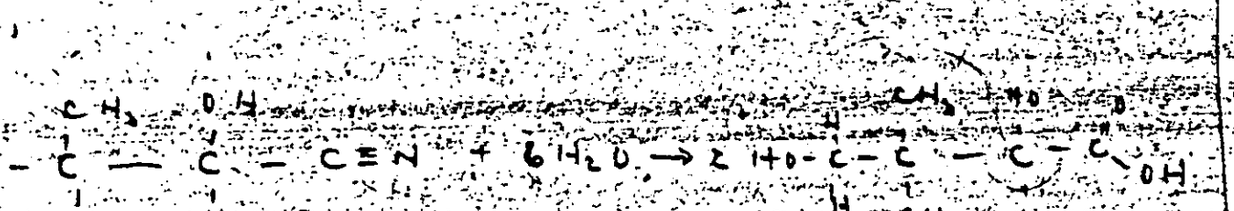
1. Reaction



α, α - Dimethyl - β - hydroxy - propionaldehyde

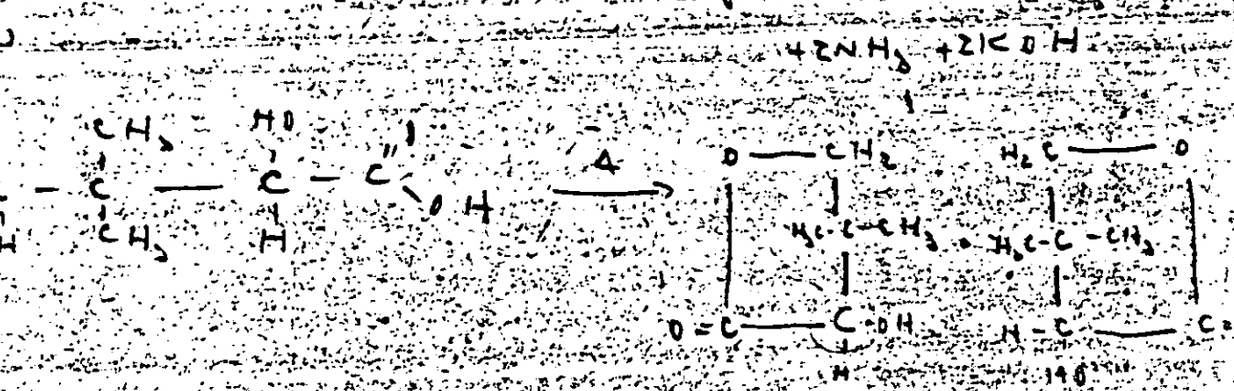
KCN addition product of α, α - Dimethyl - β - Hydroxy - propionaldehyde

and,



d, l - α - Hydroxy - β, β - Dimethyl - γ - Butyric acid

Then,



d, l - α - Hydroxy - β, β - Dimethyl - γ - Butyrolactone

2. Reactants

α,α-Dimethyl-β-hydroxy-propionaldehyde

potassium cyanide

water

3. Reagents

calcium chloride

oxalic acid

4. Yield

79%

5. Unit operations

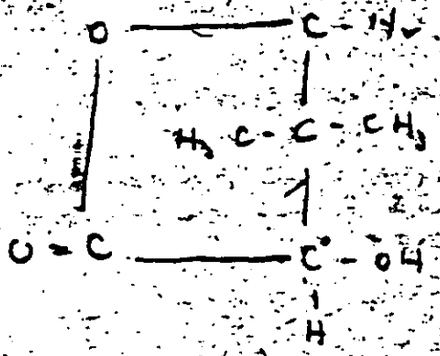
A10 - B0 - L3 - D3 - E1 - H1 - I1 - J6 - L2 - N1 - P5

6. Solvents

acetone

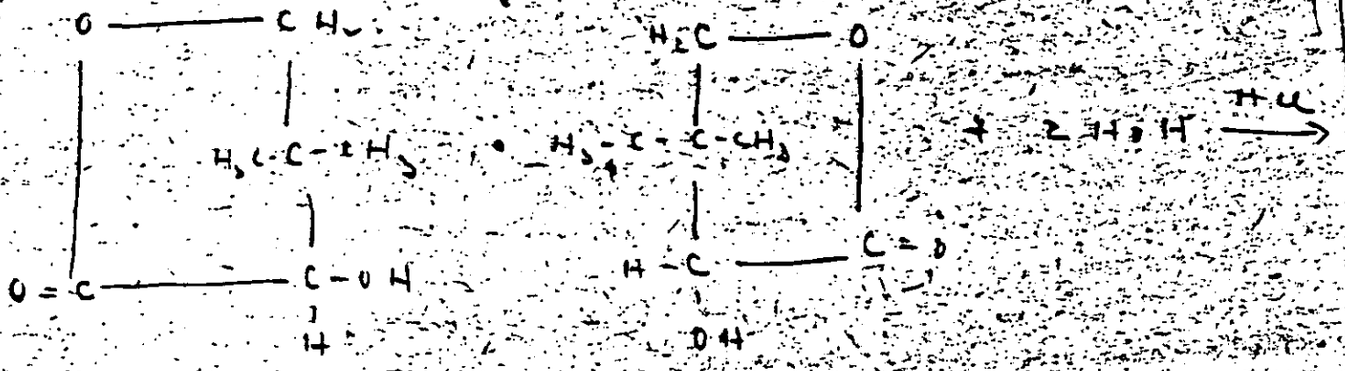
Ethyl ether

Petroleum ether

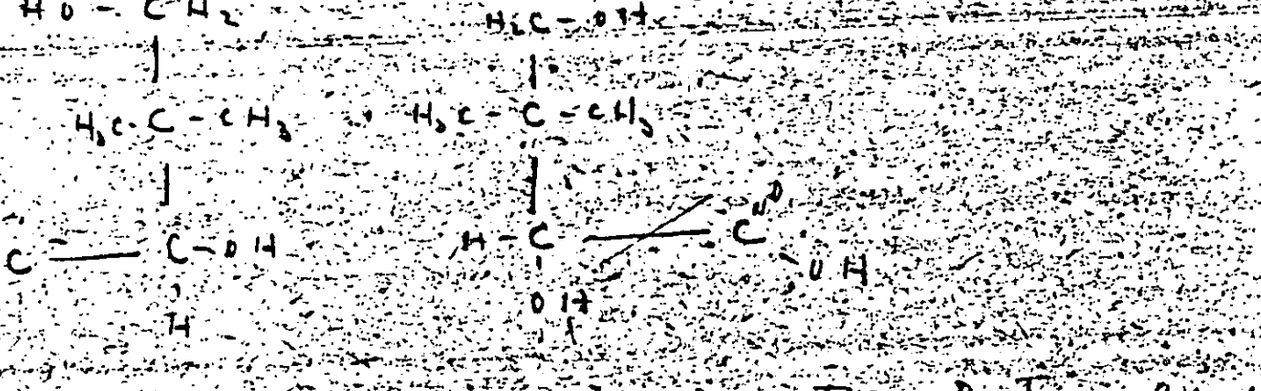


(-) α - Hydroxy - β, β - Dimethyl - γ - Butyrolactone

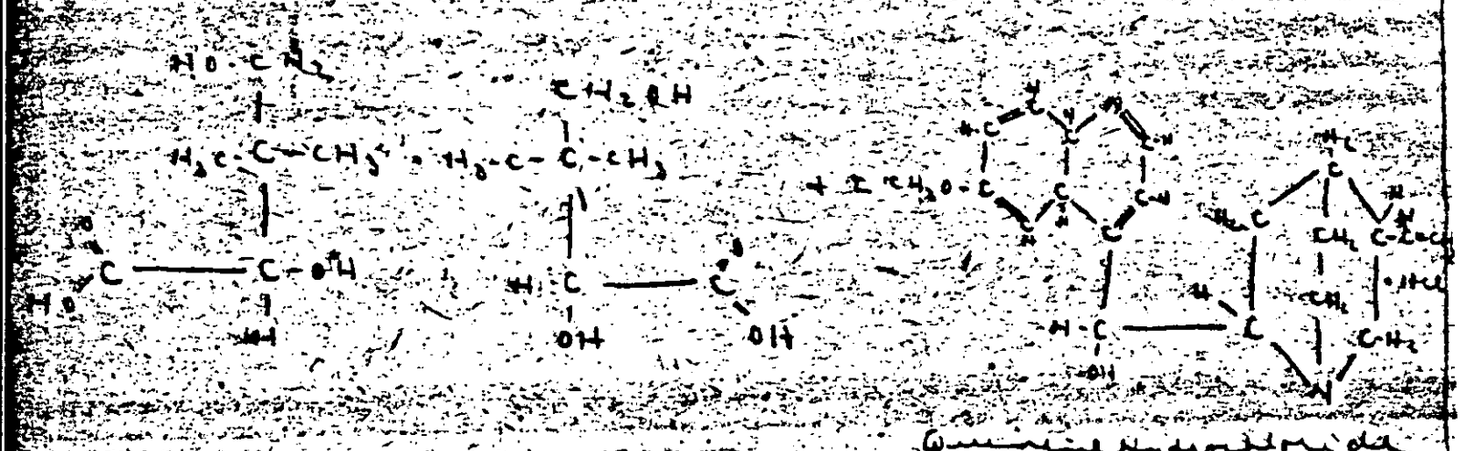
1. Reaction



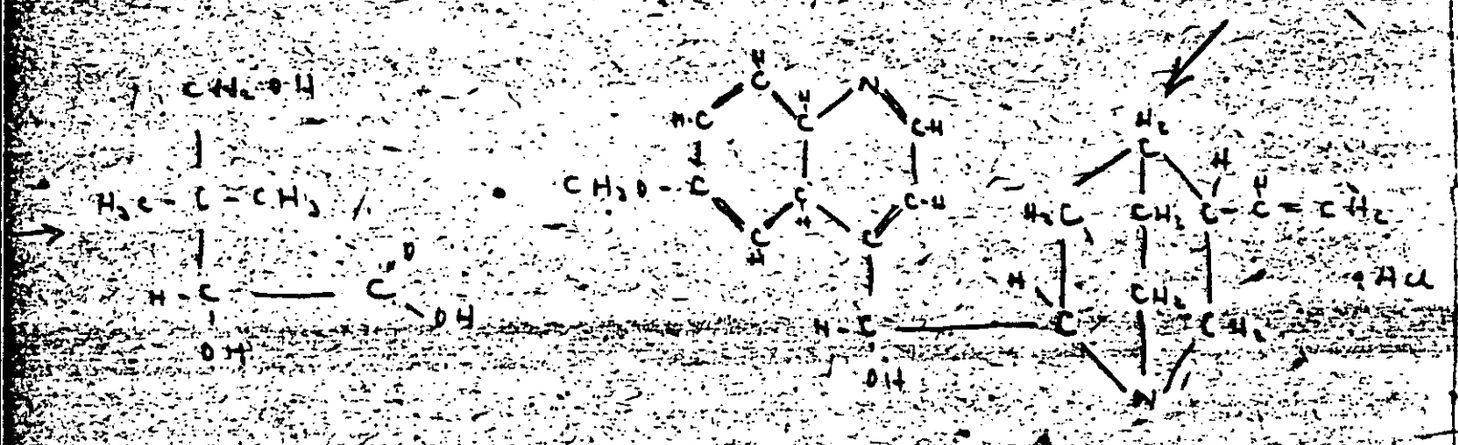
d, l - α - Hydroxy - β, β - Dimethyl - γ - Butyrolactone



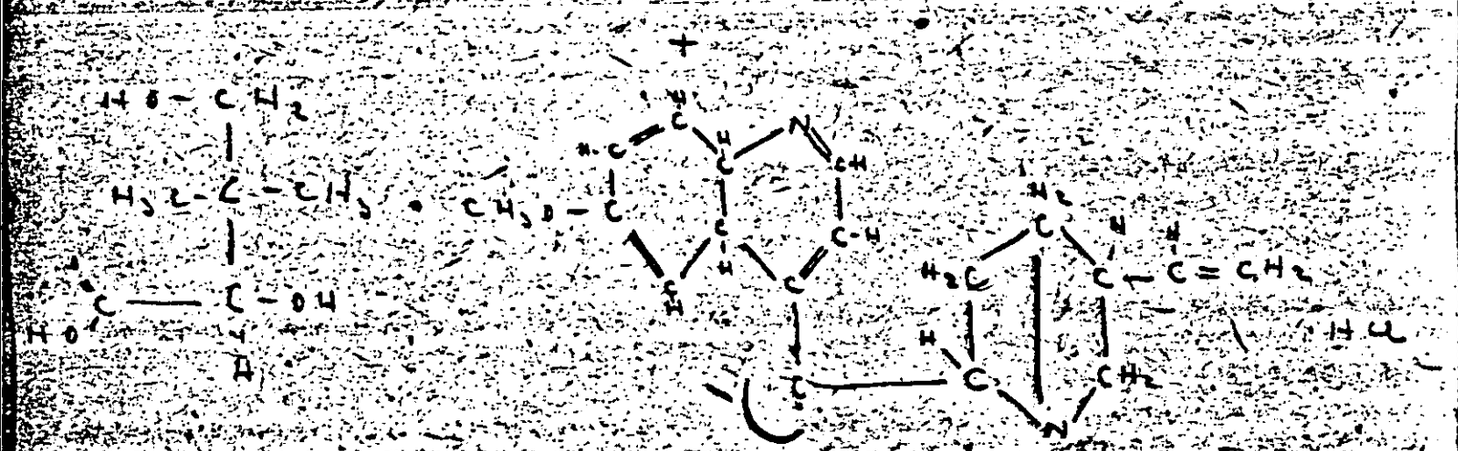
d, l - α, γ - Dihydroxy - β, β - Dimethyl - Butyric acid



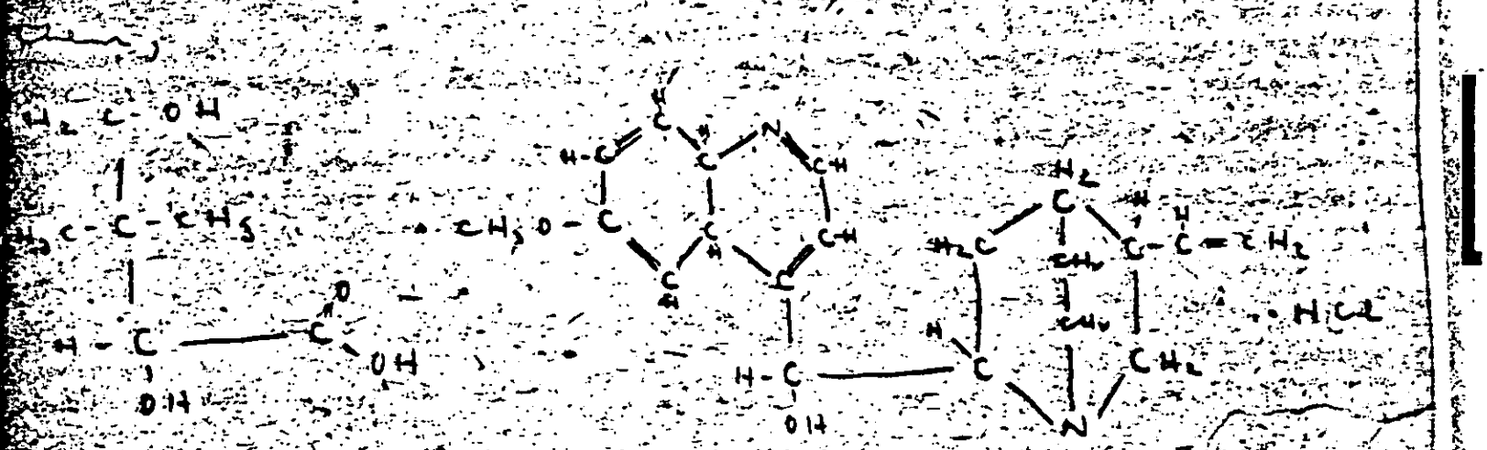
Quinine Hydrochloride



Quinine salt of (+) α,β-Dihydroxy-β,β-Dimethyl-Butyric acid
(Chemically Soluble in H_2O)



Quinine salt of (-) α,β-Dihydroxy-β,β-Dimethyl-Butyric acid
(Soluble in H_2O)



Quinine salt of (+) α,γ-Dihydroxy-β,β-Dimethyl-Butyric acid

(+) α-Hydroxy-β,β-Dimethyl-γ-Butyrolactone

2. Reactants

dl-α-Hydroxy-β,β-Dimethyl-γ-Butyrolactone

Quinine Hydrochloride

3. Reactants

Solution Hydrochloride

Hydrochloric acid

4. Yield

31-35

5. Unit operations

A-1 - D3 - C7 - D3 - E5 - H2 - I2

J3 - L3 - N3 - P10

6. Solvents

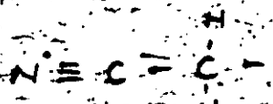
Cold Ether

Cold alcohol

Benzol

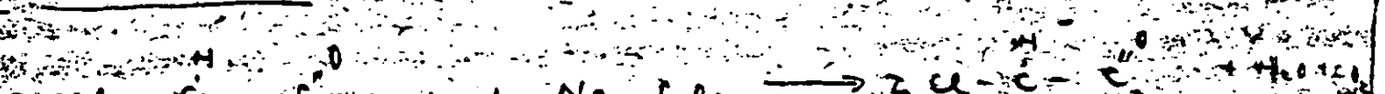
Step, β-1

monochloro acetic acid



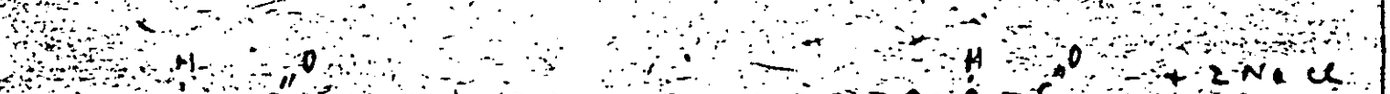
Cyano ethyl acetate

Reaction



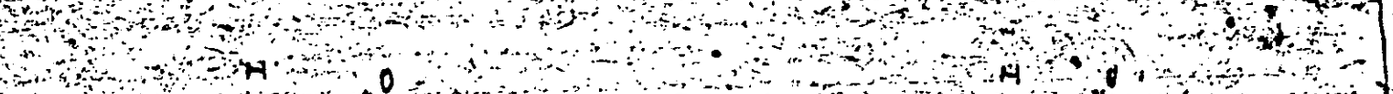
monochloro acetic acid

and,



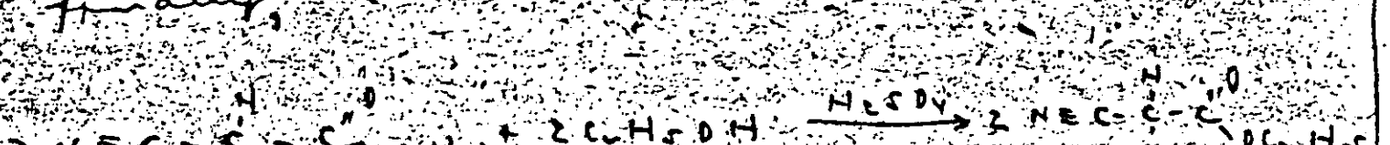
Na salt of cyano acetic acid

then,



cyano acetic acid

finally,



cyano ethyl acetate

2. Reactants

monochloro acetic acid
Sodium cyanide
Ethyl alcohol

3. Reagents

Sodium carbonate
Hydrochloric acid
Sulfuric acid

4. Yield

77%

5. Unit operations

$A_{12} - B_2 - C_9 - D_2 + E_1 - H_3 - J_9 - L_2 - P_{16}$

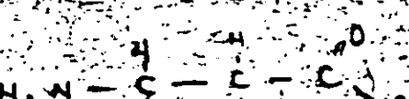
6. Solvents

Ethyl alcohol (95%)
Benzene

Step 2

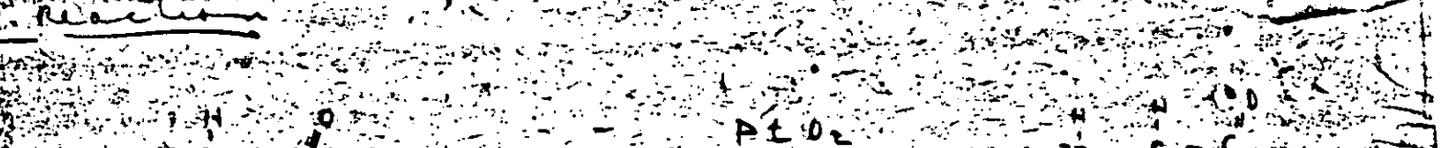
Cyano-Ethyl acetate

P.A.



β-alanine Ethyl Ester

1. Reaction



Cyano-Ethyl acetate

β-alanine Ethyl Ester

2. Reactants

Cyano-Ethyl acetate

Hydrogen

3. Reagents

platinum oxide (catalyst)

Sulphuric acid

acetic acid

Sodium Hydroxide

Potassium Carbonate

4. Yield

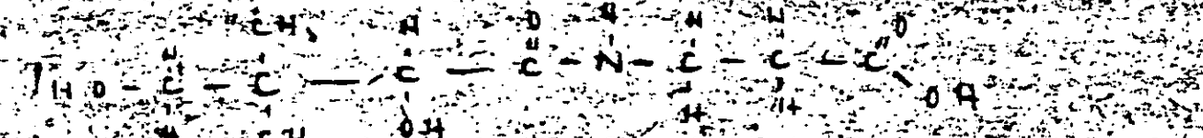
74%

5. Unit operations

A1 - B1 - C1 - D2 - E1 - G1 - H1 - J6 - L1 - P1

6. Solvents

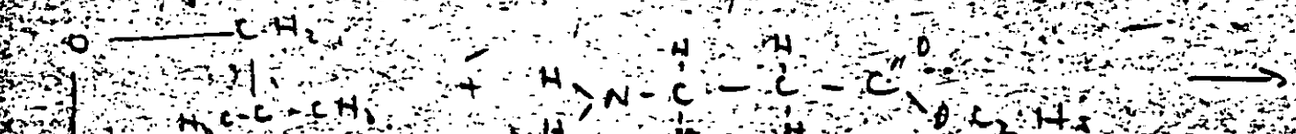
Ethyl Ether



(+) Pantothenic acid

(+) - 2,4 - Dihydroxy - P,P - Dimethyl - Butyryl - β - alanide

Reaction



(-) 2 - Hydroxy - β,β - Dimethyl - γ - Butyrolactone

β - alanine Condensation

(+) Pantothenic acid Condensation

and

(+) Pantothenic acid

(+) - 2,4 - Dihydroxy - β,β - Dimethyl - Butyryl - β - alanide

2. Reactants

(-)-α-Hydroxy-β,β-Dimethyl-γ-Butyrolactone
β-alanine Ethyl ester
Water

3. Reagents

Barium Hydroxide
Sulfuric acid
Pyridine

4. Yield

6.1%

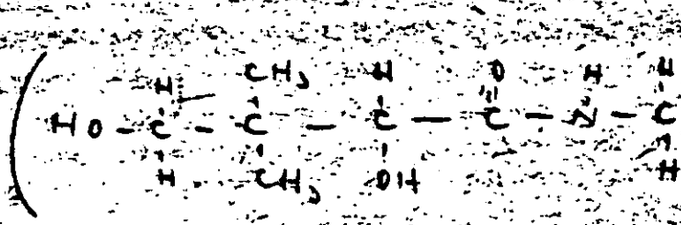
5. Unit operations

A_{22} - D_1 - C_3 - D_4 - E_3 - I_3 - J_{19} - L_4 - N_1 - P_{23}

6. Solvents

Methyl alcohol
Acetone
Ether

Step 5

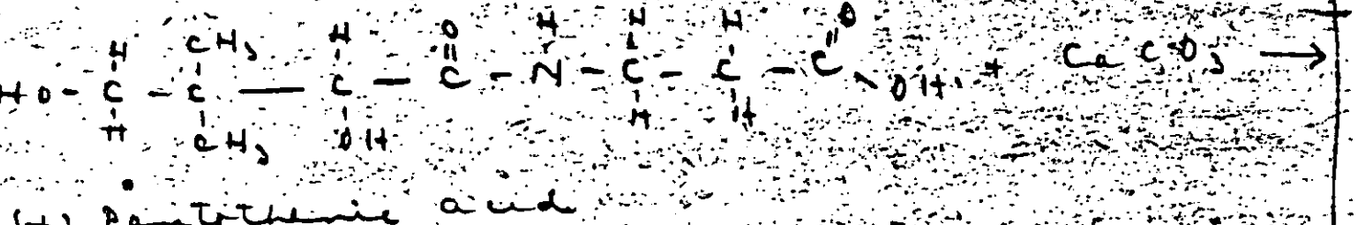


(+) Calcium Pantothenate

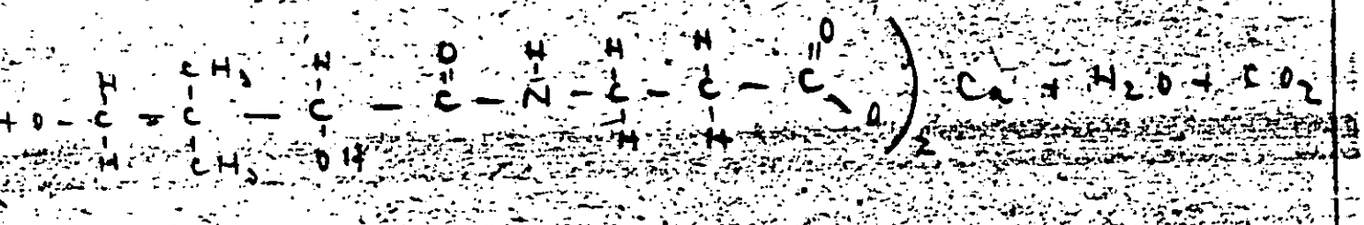
or

Ca salt of (+)-α,γ-Dihydroxy-β,β-Dimethyl-Butyryl-β-alanine

1. Reaction



(+) Pantothenic acid



(+) Calcium Pantothenate

or

Ca salt of (+)-α,γ-Dihydroxy-β,β-Dimethyl-Butyryl-β-alanine

2. Reactants

(+) Pantothenic acid

Calcium Carbonate

3. Reagents

None

4. Yield

82%

5. Liquid operations

A - Br - D - I - J - N - P

6. Solvents

Methyl alcohol

Lab 1	Lab 2	Lab 3
A II	A III	A III
B II	B II	B II
C III	C III	C II
D II	D III	D III
E I	E I	E I
H I	H I	H II
I I	I I	I II
J II	J III	J III
L I	L II	L III
N II	N I	N III
P II	P III	P III

Cap 1

A ||||| ||||

B ||

C ||||

D ||

E |

H |||

J ||||

L ||

P ||||| |

Cap 2

A ||||

B |||

C |

D ||

E |

G |

H |

J |

L |

P ||||

Cap 3

A ||||| ||||| ||

B |

C ||

D ||||

E |||

H |||

J ||||| ||||| |||

L |||||

N |

P ||||| ||||| |||

Cap 4

A |||||

B |

D |

I |

J ||||

L |||

P ||

materials used in Part A

material	gm
1-butyraldehyde	0.29
Formalin (40% formaldehyde)	0.32
K_2CO_3	2.93
monochloro acetic acid	3.16
Na_2CO_3	1.93
NaCN	9.30
HCl, 36.7%	4.61
KCN	1.024
$CaCl_2$	0.46
$CaC_2O_4 \cdot 2H_2O$	0.52
NaOH	0.94
Hydrogen	0.11
Quinine hydrochloride	0.16
$Ba(OH)_2 \cdot 8H_2O$	6.57
Pyridine	0.32
$CaCO_3$	0.32

PA → P=A

4.19.4 (3.20) = 3.59 # PA ⇌ 1.1 # PA

217.6 (0.82)

1.0 = 2.59 — 1.027 # $CaCl_2$ ⇌ 0.32 # CaO

3.8

P-Synthesis

120.1 (1.61) · 3.59 = 3.49 # (-) Nitrodiacetone

⇌ 1.09 # (-) Nitrodiol

7.5 = 3.49 # — 6.97 # P-aldimine, crude ether

3.75 ⇌ 2.18 # P-aldimine, crude ether

21.5 = 3.49 × 1.05 = 20.5 # $Na(H)_2 \cdot 3H_2O$ ⇌ 6.57 #

3.75

3.83 × 1.34 = 3.49 × 1.05 = 6.89 # H_2SO_4 ⇌ 2.15 #

3.75

120.5 × 0.05 (5.71) = 7.03 # Pyridine ⇌ 0

P-aldimine ether

113.1 (0.74) · 6.97 = 9.09 # Cyano-acid-acetate

⇌ 2.84 # Cyano-ethyl-acetate

1.06 × 9.09 = 1.1 = 0.353 # H_2 ⇌ 0.11 # H_2

3.0

.82 × 9.09 = 0.252 # NaOH ⇌ 0.79 # NaOH

1.0

2.50 × 9.09 = 7.58 # K-SG ⇌ 23.7 # K_2CO_3

3.0 ⇌ 1.79 # H_2SO_4

d,l-Methionine

$\frac{132.1}{150.1\ (0.71)} \times 3.49 = 1.72$ # d,l-Methionine

≈ 0.35 # d,l-Methionine

$\frac{7.13}{21} \times 1.13 = 0.384$ # NaOH $\approx$ 0.12 # NaOH

$\frac{18.45 \times 1.19}{21} \times 1.13 = 1.183$ # HCl $\approx$ 0.37 # HCl

$\frac{9.6 - (3.07 \times 0.72)}{21} \times 1.13 = 0.517$ # Quinine HCl $\approx$

0.16 # Quinine HCl

para d,l-Methionine

$\frac{102.1}{150.1 \cdot (0.79)} \times 1.13 = 1.12$ # α,α-Dimethyl-β-OH-propionaldehyde

$\approx$ 0.35 #

$\frac{98}{102} \times 1.12 = 1.08$ # KCN $\approx$ 0.34 # KCN

$= 1.46$ # $CaCl_2$ $\approx$ 0.46 # $CaCl_2$

$\frac{133}{102} \times 1.12$

$= 1.46$ # $CaCl_2 \cdot 2H_2O \approx$ 0.52 #

$\frac{151}{102} \times 1.12$

para-α-Dimethyl-β-OH-Butyraldehyde

$\frac{72.1}{112.1\ (0.76)} \times 1.12 = 0.92$ # Isobutyraldehyde $\approx$

0.29 # Isobutyraldehyde

$\frac{224}{200} \times 0.92 = 1.03$ # Formalin $\approx$ 0.32 # Formalin

(40%)

$\frac{153}{200} \times 0.92 = 0.736$ # $K_2SO_4 \approx$ 0.23 # K_2SO_4

$\frac{102.1}{130.1 \times (0.79)} \times 1.12 = 1.12$ # of [illegible]

[illegible] Nitrobenzene

$\frac{98}{102} \times 1.12 = 1.08$ # KCN

$\frac{155}{146} \times 1.12 = 1.48$ # $CaCl_2$

$\frac{151}{112} \times 1.12 = 1.66$ # $CaC_2O_4 \cdot 2H_2O$

$\frac{72.1}{102.1 \times (0.86)} \times 1.12 \times 0.92 =$ Isobutyraldehyde

$\frac{44}{200} \times 0.92 = 1.03$ # Formalin (40%)

$\frac{160}{200} \times 0.92 = 0.74$ # K_2CO_3

$\frac{94.5}{113.1 \times (0.77)} \times 9.79 = 9.79$ # monochloroacetic acid

≈ 5.06 # sodium acetate

$\frac{98}{510} \times 9.79 = 6.19$ # Na_2CO_3 ≈ 1.95 # NaCl

$\frac{54}{510} \times 9.79 = 5.75$ # NaCN ≈ 1.80 # NaCN

$\frac{44}{500} \times 9.79 = 13.59$ # HCl (10%) ≈ 4.24 # HCl

$\frac{44}{500} \times 9.79 =$ [illegible] ≈ 4.41 # $C_{11}H_{21}N$

$\frac{0.3 \times 900}{500} =$

$\frac{113}{117.1}$ (0.7 H) = 9.16 M

cyano-ethyl-acetate

$\frac{1.06}{30} \times 9.16 =$ 0.253 M HCl (10.5 ml = 0.264 eq)

$\frac{0.93}{30} \times 9.16 =$ 0.253 M NaOH

$\frac{250}{30} \times 9.16 =$ 76.30 g K-CO$_3$

$\frac{130.1}{130.1} \times \frac{}{0.31} \times 3.51 =$ 1.13 lb

di-butyrolactone

$\frac{7.15}{21} \times 1.15 =$ 0.391 M NaOH

$\frac{1.45 - 1.19 = 0.26}{21} \times 1.15 =$ 0.03 M HCl (13.20)

$\frac{9.6 (10.7 - 7.4)}{21} \times 1.15 =$ 0.517 M Quinic Acid

$\frac{1.7 \times 1.19 \times 0.36}{21} \times 1.15 =$ 0.392 M HCl (36.2%)

A Fluid Transfer (Liquid + Solid)

B Solids Transfer (conveying)

C Heat Transmission

D Evaporation

E Extraction

F Adsorption

G Gas Absorption

H Distillation

J Drying

I Agitation

K Crushing + Grinding

L Filtration

M Classification

N Crystallization

O Sublimation

P Proportioning + Weighing (Liquids + Solids)

Q Air Conditioning (Temp + Humidity regulation)

DL-ALANINE

(α-Aminopropionic Acid)

Submitted by Hal T. Clarke and Ernest Dyer Bean.
Checked by W. Alfred B. Coleman and W. L. McEwen.

1. Procedure

To a cold (0–5°) solution of 90.2 g. (1.61 moles) of potassium hydroxide (sticks) in 375 cc. of distilled water is added slowly with stirring 96.6 g. (30.8 cc., 0.605 mole) of bromine. This solution is chilled to 0° and 50.1 g. (0.6 mole) of succinimide (p. 75) is added with hand stirring. The mixture is warmed in a water bath to 55–60°, when it becomes colorless, and is held at that temperature for two hours (Note 1). After being allowed to stand overnight at room temperature, it is acidified to Congo red with concentrated hydrochloric acid (about 280 cc., sp. gr. 1.18) (Note 2) and evaporated to dryness on a steam bath under reduced pressure. The residue is treated with 1 l. of warm 95 per cent alcohol; the undissolved potassium bromide is filtered off and washed with 50–100 cc. of cold alcohol in small portions. The filtrate and washings are combined and evaporated to dryness under reduced pressure, and the residue is extracted with 400 cc. of 95 per cent alcohol. The resulting solution is again evaporated to dryness and the residue finally extracted with 250 cc. of hot absolute alcohol (Note 3). After distilling off the bulk of the alcohol, this

extract is diluted with about 500 cc. of distilled water and shaken out twice with 200-cc. portions of ether. The ether extracts are discarded (Note 4).

The aqueous solution is freed of ether and alcohol and then boiled under reflux for one to one and a half hours in order to hydrolyze any β-alanine ester. After evaporating under reduced pressure to remove as much as possible of the excess hydrochloric acid, the residue is dissolved in water and diluted to exactly 1000 cc. A 5-cc. portion of this solution is withdrawn for determination of total halides. A suspension of silver oxide, prepared from 10 per cent more than the equivalent quantity of silver nitrate (Note 3) is added to the remaining portion of the solution, and the mixture is stirred well in order to bring about complete precipitation of the halides. After standing overnight the precipitate is filtered off and washed with water. The filtrate and washings are concentrated under reduced pressure to about 500 cc., saturated with hydrogen sulfide, and filtered through a thin layer of decolorizing carbon. The colorless filtrate is evaporated to a volume of about 300 cc., treated with decolorizing carbon if necessary, concentrated on the steam bath until crystallization begins, and chilled. The crystals are filtered with suction, washed with a little cold alcohol, and dried. A further crop is obtained by concentrating the mother liquor and again chilling (Note 6). The combined crops (28–30 g., m.p. 189–191°) are recrystallized from water, employing the same procedure, and yield 23–24 g. (41–43 per cent of the theoretical amount) of pure β-alanine, which melts at 197–198° (corr.) with decomposition. About 2 g. of less pure product can be secured from the final mother liquors.

Notes

1. The odor of ammonia is perceptible, indicating some hydrolysis.

2. On acidification a small amount of bromine may be liberated; this is removed rapidly during the subsequent evaporation.

3. In the last extraction the alcohol-insoluble material may be removed advantageously with a centrifuge.

[5] This ether extraction removes small quantities of succinic acid and its esters.

[6] The silver oxide is prepared by dissolving the silver nitrate from about five parts of cold water and adding a slight excess of pure sodium hydroxide in 10 per cent solution. The precipitate is well stirred, collected by filtration or centrifuging, and washed free of sodium salts. It should not be dried before use.

[7] The final mother liquor consists of a rather viscous solution containing uncrystallizable by-products.

Methods of Preparation

The above directions are based upon the methods of Hoogewerff and Van Dorp,[1] as modified by Holm[2] and by Hale and Hoover.[3] β-Alanine has also been prepared by the action of hypobromite upon succinimide and hydrolysis of the resulting β-ureidopropionic acid,[4] by the action of ammonia upon β-iodopropionic acid,[5] by the hydrolysis of methyl carbomethoxy-β-aminopropionate, obtained by the action of sodium methoxide on succinbrommide,[6] by the reduction of β-nitropropionic acid,[7] by heating ethyl acrylate with alcoholic ammonia,[8] from succinyl-glycine ester by the oxide synthesis,[9] and by the action of liquid ammonia upon methyl acrylate.[10]

[1] Hoogewerff and Van Dorp, *Rec. trav. chim.* **10**, 5 (1891).

[2] Holm, *Arch. Pharm.* **242**, 597 (1904).

[3] Hale and Hoover, *J. Am. Chem. Soc.* **32**, 774 (1910).

[4] Weidel and Roithner, *Monatsh.* **17**, 777 (1896).

[5] Henle, *Ann.* **256**, 25 (1890); Balbiano, *Ber.* **9**, 1902 (1876); Abderhalden and Eichwald, *Z. physiol. Chem.* **88**, 414 (1913).

[6] Hoogewerff and Juteglitte, *Ann. Chem.* **263**, 1 (1891); **264**, 304 (1891).

[7] Hoogewerff, *Ann.* **264**, 368 (1891).

[8] Wender, *Pract. Chim. Sal.* **22**, 457 (1889).

[9] Curtius and Hochstetter, *J. prakt. Chem.* [2] **103**, 289 (1921).

[10] Lorenz, *Z. Elektrochem.* **28**, 1 (1922).

structure factors remain essentially constant).

The values in Table I show that the melting points decrease markedly with increasing size of the alkyl groups.

TABLE I

MELTING POINTS OF VARIOUS ALKYLATED AMINO NITRO COMPOUNDS

Compound	M. p., °C.
Nitroaminodurene	[illegible]61
Nitrodimethylaminodurene	[illegible]90
1-Amino-4-nitronaphthalene	191
1-Methylamino-4-nitronaphthalene	[illegible]
1-Ethylamino-4-nitronaphthalene	[illegible]
1-Benzylamino-4-nitronaphthalene	[illegible]
1-Dimethylamino-4-nitronaphthalene	[illegible]
1-Diethylamino-4-nitronaphthalene	Liquid

There is no chance for a preferred position of the alkyl groups in this case.

SCHOOL OF CHEMISTRY RICHARD T. ARNOLD
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RECEIVED MAY [illegible], 1940

THE BIOLOGICAL ACTIVITY OF SYNTHETIC PANTOTHENIC ACID

Sir:

The lactone of the acid fragment of pantothenic acid has been identified as α-hydroxy-β,β-dimethylbutyrolactone by Stiller, Keresztesy and Finkelstein.[1] The coupling of the synthetic *dl*-lactone with β-alanine in 50% yields, as determined by microbiological assay and assuming the inactivity of one isomer, has been reported by Weinstock and co-workers.[2] In the present investigation the yield from the coupling reaction was 88% and definite evidence was found for the inertness of the unnatural isomer.

When equimolecular amounts of 1 N sodium hydroxide, β-alanine and the lactone are mixed at 70°, 50% coupling takes place almost immediately as determined by a Sörensen formol titration for free amino nitrogen. Upon standing no further coupling occurs. Instead, the remaining hydroxide ion disappears during the course of an hour, due probably to the saponification of the uncoupled lactone. If instead of equimolecular amounts, the ratio of lactone to β-alanine to 1 N sodium hydroxide is made 3:1:1, a 65% coupling occurs immediately, again followed by the disappearance of hydroxide ion. If now to this same solution an amount of 10 N sodium hydroxide equivalent to the amount of free β-alanine remaining is added, 51% of this remainder likewise couples. Upon repetition of the procedure, the % of the remainder of the β-alanine which couples falls off rapidly. The results of a typical experiment are summarized in Table I.

TABLE I

	[illegible]	Equivalents of hydroxide [illegible]	[illegible]	Total [illegible] %
Present at start	[illegible]	[illegible]	[illegible]	[illegible]
Present after 1 hr.	[illegible]	[illegible]	[illegible]	[illegible]
Added at end of 1 hr.	[illegible]	[illegible]	[illegible]	[illegible]
Present at end of 2 hr.	[illegible]	[illegible]	[illegible]	[illegible]
Added at end of 2 hr.	[illegible]	[illegible]	[illegible]	[illegible]
Present at end of 3 hr.	[illegible]	[illegible]	[illegible]	[illegible]
Added at end of 3 hr.	[illegible]	[illegible]	[illegible]	[illegible]
Present at end of 4 hr.	[illegible]	[illegible]	[illegible]	[illegible]

[a] By Sörensen formol titration. [b] Acid to phenolphthalein. [c] By difference.

At the end of the experiment, the solution was biologically assayed with chicks,[3] and found to contain 3,680,000 chick filtrate factor units, corresponding to 36 units per mg. of *dl*-pantothenic acid. Natural pantothenic acid has been stated to contain 71 chick units per mg.[3] This points to the inactivity of one enantiomorph in the synthetic preparation.

At the same time a mixture of 10 g. of the *dl*-lactone and 7 g. of β-alanine was incorporated in 1000 g. of heated diet and biologically assayed. Slight but definite activity was observed, calculated to correspond roughly to a coupling in vivo of 0.06% of the mixture. This indicates that none of the activity of the pantothenic acid solution at the level fed (corresponding to 2.4 mg. of *dl*-pantothenic acid per 100 g. of diet) may be attributed to the presence of unchanged starting materials.

(1) [illegible], THIS JOURNAL, [illegible]
(2) Weinstock, May and Arnold, [illegible], 111 (1940).
(3) [illegible]
(4) [illegible] 223 (1939).

DIVISION OF CHEMISTRY AND POULTRY HUSBANDRY
UNIVERSITY OF CALIFORNIA S. H. BABCOCK, JR.
COLLEGE OF AGRICULTURE T. H. JUKES
DAVIS, CALIFORNIA

RECEIVED MAY 20, 1940

NAPHTHOQUINONE OXIDES

Sir:

Since 2-methyl-1,4-naphthoquinone oxide can be converted very easily and efficiently [Fieser, *J. Biol. Chem.*, 133, 391 (1940)] into the isomer phthiocol, it was somewhat surprising to discover

Total Synthesis Experiments

Summary

Received May 10, 1940

Pantothenic Acid. VIII. The Total Synthesis of Pure Pantothenic Acid

moved by distillation under reduced pressure, and then 75 cc. of dry ether was added, the lead salts filtered off and washed thoroughly with anhydrous ether. The combined filtrate and washings were evaporated to dryness in vacuum at [illegible]. The residue (304 mg.) was an almost colorless oil which gave a strong positive test for an aldehyde with Schiff reagent.

The aldehyde (304 mg.) was dissolved in 15 cc. of absolute alcohol, and a solution of 2 g. silver nitrate (calcd. [illegible]) in 10 cc. of water added. During a half hour a 0.5 N aqueous solution of 0.71 g. sodium hydroxide (calcd. 0.705 mg.) was added dropwise with vigorous stirring. There was an immediate formation of a black precipitate of silver, and after the final addition of alkali, the stirring was continued for three hours. The silver was removed by filtration and thoroughly washed with water. The filtrate, which was slightly alkaline and gave a negative Schiff test, was evaporated at 30° under reduced pressure to 10 cc. It was acidified to pH 2.3 with dilute sulfuric acid and continuously extracted with ether for sixteen hours. The ether extract was dried thoroughly with sodium sulfate and then evaporated to dryness. The residue was a pale yellow viscous oil which crystallized on standing, yield 330 mg. After recrystallization from ether–petroleum ether, it was obtained as colorless needles, m. p. 124–125°; mixed m. p. with an authentic specimen of hydroxypivalic acid 124–125°.

Anal. Calcd. for $C_5H_{10}O_3$: C, [illegible]; H, 8.5. Found: C, 50.78; H, 8.60.

Acknowledgments.—The authors wish to express their great appreciation to Dr. R. J. Williams for making available to them much unpublished work and for much helpful advice. They further wish to acknowledge their appreciation for the help given by Messrs. E. F. Pratt and H. K. Mitchell during the summer of 1939. They also wish to express their indebtedness to Drs. R. T. Major and K. Folkers for their interest and advice, to Messrs. D. F. Hayman and W. Reiss and H. S. Clark for carrying out the microanalyses and to Messrs. A. Nash, H. Koones, B. Ricks and W. B. Wright for their assistance throughout the investigation.

Summary

1. Concentrates of pantothenic acid have been prepared, and from the hydrolyzates of these concentrates a crystalline lactone has been isolated.

2. The lactone has been characterized as the lactone of α,γ-dihydroxy-β,β-dimethylbutyric acid by degradative methods.

3. Pantothenic acid is (+)-α,γ-dihydroxy-β,β-dimethylbutyryl-β'-alanide

$$HOCH_2-\underset{CH_3}{\overset{CH_3}{C}}-CHOH-CONH-CH_2-CH_2-COOH$$

RAHWAY, N. J. RECEIVED MAY 10, 1940

[CONTRIBUTION FROM THE [illegible] LABORATORIES OF [illegible] STATE COLLEGE AND THE UNIVERSITY OF TEXAS]

Pantothenic Acid. VII. Partial and Total Synthesis Studies

BY ROGER J. WILLIAMS, HERSCHEL K. MITCHELL, HARRY H. WEINSTOCK, JR., AND ESMOND E. SNELL

Partial Synthesis Experiments

The fact that a partial synthesis of pantothenic acid was first accomplished in June, 1938, has been alluded to,[illegible] since subsequent to the identification of the lactone moiety[illegible] the method used in this partial synthesis served as a basis for a practical synthesis it is desirable to record the details of this earlier work.

Our previous finding that the non-nitrogenous cleavage product of pantothenic acid was a lactone[illegible] led us to attempt to produce the ester of pantothenic acid by the aminolysis of this lactone (the exact structure of which was not known) as follows:

$$CH_2-R-CHOH-CO\ (\text{lactone, }-O-) + H_2NCH_2CH_2CO_2Et \longrightarrow \underset{OH}{CH_2}-R-CHOH-CONHCH_2CH_2CO_2Et$$

Methods for hydrolyzing the ester of pantothenic acid without cleavage of the peptide linkage have previously been reported.[illegible] Such experiments were found to be successful and yields up to approximately 50% of theoretical were obtained, calculated on the basis of original pantothenic acid from which the impure lactone for the reaction was derived. An example is cited below.

Calcium pantothenate, [illegible] of potency [illegible]200, was heated at 100° for one-half hour with 1.1 ml. of 0.5 N hydrochloric acid. A 0.15-ml. portion equivalent to 150 [illegible] of the [illegible] and evaporated [illegible]

[illegible]

[illegible] change, indicating that at least partial racemization was taking place.

The pure (−)lactone had the same melting point, mixed melting point and specific rotation, and gave the same p-nitrobenzoate as was obtained from the lactone derived from natural pantothenic acid, thus proving their chemical identity.

The synthetic (−)rotatory, (+)rotatory and racemic forms of the lactone were condensed with β-alanine ester and purified by the method described above and gave the synthetic (+)rotatory, (−)rotatory and racemic pantothenic acids, respectively. These acids, like the one derived from the natural lactone, were obtained as viscous oils. The free acids are difficult to free from the last traces of solvents and hence physical constants made on such viscous oils may vary. They form, however, microcrystalline calcium salts which do not have definite melting points but decompose with evolution of gas at temperatures between 150 and 160°. Bacterial assays of these products showed that the (+)pantothenic acid had the full activity of the natural vitamin, whereas the (−)form was inactive when prepared from a rigidly purified specimen of the (+)lactone. The racemic modification had half of the activity of natural (+)form. The bacterial assay of the corresponding calcium salts gave similar results as shown in Table I.

TABLE I

COMPARISON OF PANTOTHENIC ACID WITH ITS (−) AND dl-ISOMERS

		[illegible]	[illegible]	[illegible]
(+)Form	Biosynthetic	[illegible]	[illegible]	[illegible]
	Synthetic	[illegible]	[illegible]	[illegible]
(−)Form		[illegible]	[illegible]	[illegible]
Racemic		[illegible]	[illegible]	[illegible]

All the calcium salts were [illegible]. The difficulty encountered in thoroughly drying these viscous oils probably accounts for the low assay values. The bacterial assay values are compared with a standard sample of a pantothenic acid concentrate kindly supplied by Dr. R. J. Williams. Equimolecular mixtures of (+) and (−)calcium pantothenate were assayed and they showed [illegible]% activity.

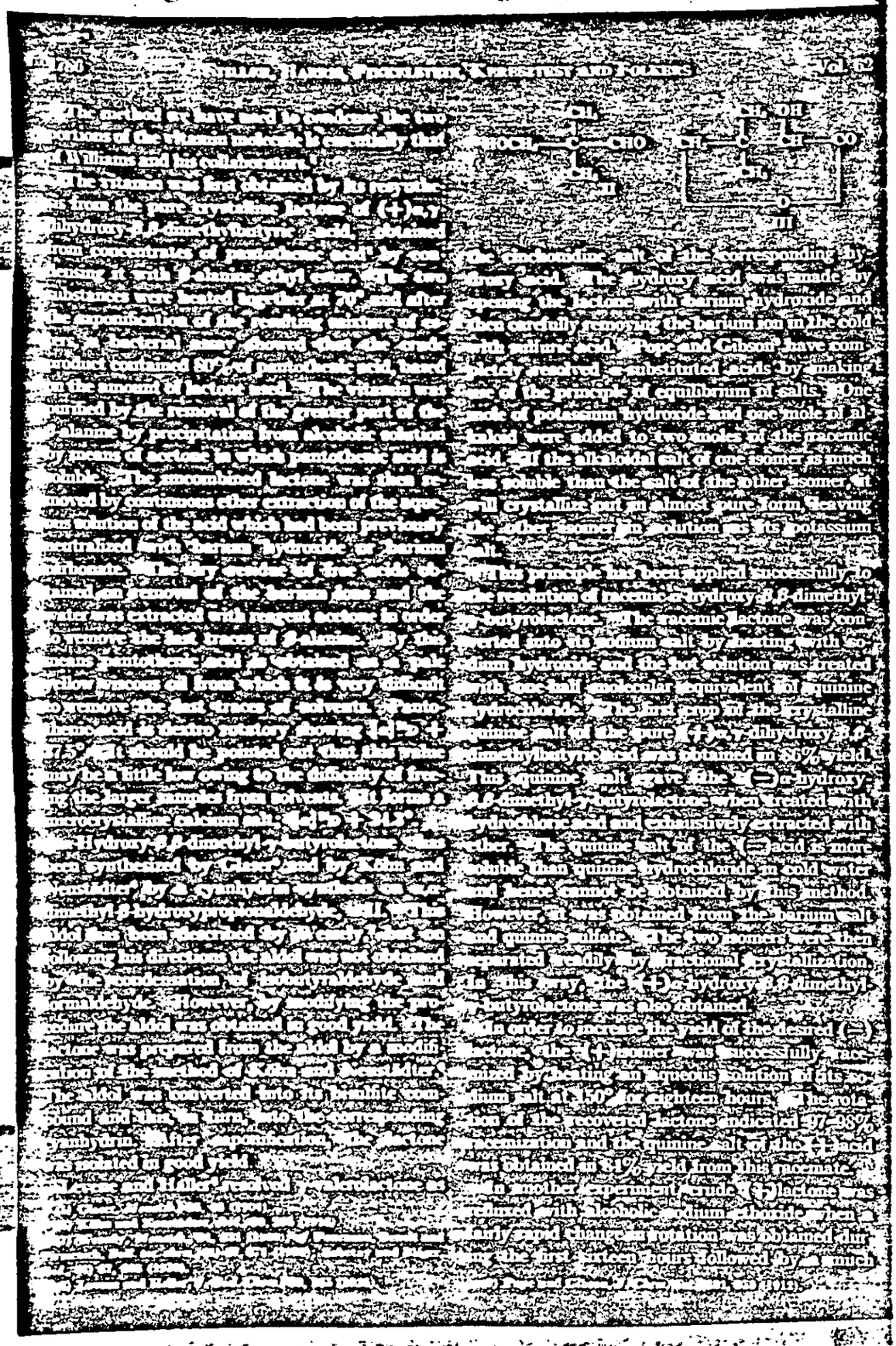
We are indebted to Dr. Klaus Unna of the Merck Institute for Therapeutic Research for the preliminary determination of the biological activity of synthetic (+)pantothenic acid and its (−)isomer. The synthetic (+)pantothenic acid was tested in chicks according to the method proposed by Jukes and Lepkovsky, and was found [illegible] (J. Biol. Chem., [illegible]) active in promoting growth and curing the dermatitis. The responses to 15 and 20 mg. per 100 g. of diet were not significantly different as to growth and curative effects. On the other hand, 10 mg. per 100 g. of diet produced weight increase approximately half of that obtained with the higher dose levels. A dose of 800 γ of the synthetic (+)pantothenic acid given as a single dose to pantothenic acid depleted rats produced a rapid and marked gain in weight whereas the same dose of the (−)form was practically without effect.

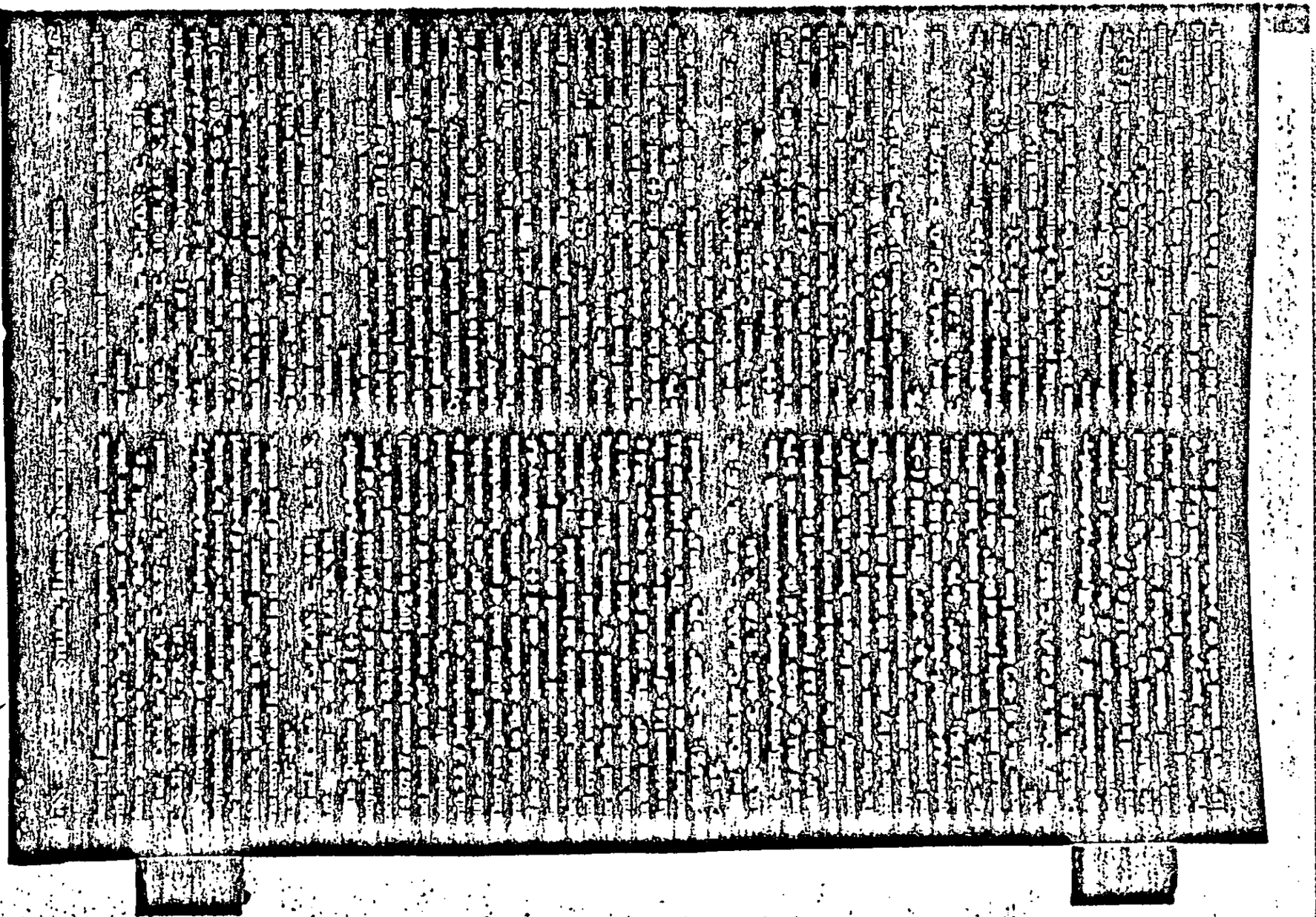
Experimental Part

α,α-Dimethyl-β-hydroxypropionaldehyde, II.—A mixture of 300 g. of isobutyraldehyde and 224 g. of 40% formalin was stirred in an ice-bath and 100 g. of potassium carbonate was added in small portions at such a rate that the temperature of the reaction mixture did not exceed 20°. After all the potassium carbonate had been added, the stirring was continued for one hour. During this period, the reaction mixture reached room temperature. The viscous liquid was extracted with ether and dried over sodium sulfate. When the ether was removed, the residue solidified upon cooling. The aldol was purified by distillation. At 15 mm. the b. p. was 83–88° and the distillate immediately crystallized. After recrystallization from alcohol, the product was dried at 60° in vacuum, m. p. 96–97°.

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.82; H, 9.80. Found: C, 59.00; H, 9.78.

Racemic α-Hydroxy-β,β-dimethyl-γ-butyrolactone, III.—A solution of 80 g. of sodium bisulfite was stirred and heated on the steam-bath with 72 g. of α,α-dimethyl-β-hydroxypropionaldehyde until complete solution was obtained. The solution was then cooled to 10° and maintained between 5–10°, while a solution of 46 g. of potassium cyanide was added slowly. The stirring was continued for one hour before removing the ice-bath and permitting the reaction mixture to reach room temperature. The upper cyanohydrin layer was separated and combined with the subsequent ethereal extractions of the aqueous portion. The ethereal solution was then added slowly to 200 cc. of concentrated hydrochloric acid while maintaining the temperature between 10–15°. After the addition, the reaction mixture was kept at room temperature overnight. A sufficient amount of water was then added to dissolve the precipitated ammonium chloride and the solution was then heated. After the ether had been removed, the hydrolysis was completed by heating at 100° for three hours. The solution was then treated in the cold with a 40% solution of sodium hydroxide until almost neutral and finally treated with a saturated solution of sodium bicarbonate until the pH was 7.2. This solution was then continuously extracted with ether for sixteen hours. The ethereal extract was dried over sodium sulfate and then fractionated. The lactone boiled between 119–121° at 13 mm. and solidified to a glassy product. It was recrystallized by dissolving in cold ether and adding cold petroleum ether until just cloudy. Upon standing





Acknowledgments.—The authors wish to express their appreciation to Dr. R. J. Williams for making available to them unpublished data and for much helpful advice. They also wish to express their indebtedness to Drs. R. S. Mayer and W. H. Peterson for their interest and counsel; to Messrs. D. F. Hayman, W. Rees, and H. S. Clark for carrying out the microanalyses; and to Messrs. G. A. Boyack, M. Kashar, Ruth Sp[illegible]ley, A. S. Swanson, and W. B. [illegible] for their assistance throughout the investigation.

Summary

[illegible]-Hydroxy-β,β-dimethyl-γ-butyrolactone has been synthesized and resolved into its optical enantiomorphs.

2. The (−)form of the lactone has been shown to be identical with the lactone obtained from the hydrolysis of pantothenic acid.

3. (+)Pantothenic acid has been synthesized from the lactone obtained from natural sources and isolated as its calcium salt.

4. (+)Pantothenic acid has been synthesized from [illegible]-hydroxy-β,β-dimethyl-γ-butyrolactone and shown to have the same physiological activity as the resynthesized pantothenic acid.

5. Racemic and (±)pantothenic acids have been synthesized from the racemic and (±)α-hydroxy-β,β-dimethyl-γ-butyrolactones and isolated as their calcium salts. They were shown to be respectively 50% and 50% of the bacterial growth stimulation activity of (+)pantothenic acid.

6. The synthetic (+)pantothenic acid showed the expected biological activity when assayed on [illegible] and rats.

[illegible] 1940

[Contribution from the Chemical Laboratory of Harvard University]

The Resolution of Racemic Pantothenic Acid by Means of Quinine Methohydroxide

By [illegible] and Arthur [illegible]

Received August 20, 1941

sample of quinine methopantothenate ($(\alpha)_D$ −118°) prepared from calcium (+)-pantothenate. It showed no depression of the m. p. Further, both samples of quinine methopantothenate showed 100% activity on bacterial assay.

Further fractionation of the original mother liquor gave two small fractions of intermediate composition and bacterial activity, and finally a third fraction which had a very low bacterial activity. This fraction after several crystallizations from alcohol-ether gave a product which had a bacterial activity of [illegible]%, $(\alpha)_D$ −150.5°, m. p. 170°. The mixed m. p. with a specimen prepared from calcium (−)-pantothenate showed no depression.

Final confirmation of the identity of the optical antimorphs was obtained by the decomposition of the alkaloidal salts followed by the conversion of the resulting (+)- and (−)-pantothenic acids into their S-benzylthiuronium salts. These were identical with specimens prepared from (+)- and (−)-pantothenic acids obtained from the enantiomorphs of the resolved α-hydroxy-β,β-dimethyl-γ-butyrolactone.

The carbon analyses of all of the samples of the quinine metho salts, both resolved and synthetic, ran consistently low (0.5–0.8%). A second resolution was, therefore, carried out using quinine methohydroxide which had been prepared from [illegible] purified quinine. The analytical results, however, again gave low carbon values.

The [illegible] pantothenic acid [illegible] resolved by means of its cinchonidine salt. After three recrystallizations from an alcohol-ether mixture, the pure cinchonidine salt of (+)-pantothenic acid was obtained ($(\alpha)_D$ [illegible]°, m. p. 170–172°). It gave no depression of m. p. [illegible] admixture with an authentic sample of the cinchonidine salt prepared from (+)-pantothenic acid. On bacterial assay it showed [illegible]% activity.

Experimental Part

[illegible]

... [illegible] g.). The solution was then evaporated to dryness below 25° and the residue was dried by dissolving in absolute alcohol (50 cc.), adding 75 cc. of benzene and removing the solvents by distillation in vacuo. The residue was finally dried in a desiccator over sulfuric acid.

The dry, partially crystalline residue was ground to a fine powder with 250 cc. of ethyl acetate in order to remove a small amount of gummy material which hindered crystallization of the product; yield, 63.8 g. This material had m. p. 177°; $(\alpha)_D$ −132.1° (c, 0.7% in MeOH); bacterial assay 60%.

By fractional crystallization of the product from 100 cc. of alcohol by the successive addition of 100-cc. portions of ether, four crops of crystals were obtained as shown in Table I.

TABLE I

Fraction	M. p., °C.	$(\alpha)_D$	Weight, g.	Bacterial assay, %
A	1[illegible]–1[illegible]	−130°	[illegible].6	[illegible]6.4
B	177	−13[illegible].5°	[illegible].7	[illegible]1.0
C	1[illegible]	−127.8°	[illegible]	[illegible]6.6
D	1[illegible]	−150.0°	[illegible].3	[illegible]

After six recrystallizations of Fraction A from the alcohol-ether mixture (1:2) 4.6 g. clusters of small, fine, colorless needles was obtained which showed 100% activity on bacterial assay. It also showed $(\alpha)_D$ −122.0° (c, 1.17% in MeOH); m. p. 190–197° with material prepared from (+)-pantothenic acid.

Anal. Calcd. for $C_{31}H_{45}O_6N_3$: C, 64.63; H, 7.72; N, 7.34. Found: C, 64.12; H, 7.90, 8.05; N, 7.48, 7.43, 7.[illegible].

Fraction D was recrystallized five times from alcohol-ether (1:20) and was then obtained in clusters of fine colorless needles, m. p. 170°, mixed m. p. with a sample prepared from (−)-pantothenic acid, 170°. It showed $(\alpha)_D$ −15[illegible]° (c, 0.90% in MeOH) and bacterial assay 0.1%; yield 4.1 g.

Anal. Calcd. for $C_{31}H_{45}O_6N_3$: C, 64.63; H, 7.72; N, 7.34. Found: C, 63.97; H, 7.97; N, 7.53.

Quinine Metho Salt of (+)-Pantothenic Acid.—A solution of 0.8[illegible] g. of calcium (+)-pantothenate in [illegible] cc. of water was treated with an equivalent amount of N sulfuric acid with cooling. The calcium sulfate was removed by [illegible] and washed with a small quantity of ice-water. The combined filtrates were adjusted to pH 6.5 with pyridine and evaporated to dryness in vacuo at 25°. The residue after drying in high vacuum was extracted with 20 cc. of acetone and the insoluble calcium sulfate removed by filtration. On removal of the acetone by evaporation in vacuo, the pure (+)-pantothenic acid was obtained as a colorless viscous oil, yield 0.8067 g.

The product was dissolved in 5 cc. of water and neutralized to pH 7.5 with an aqueous solution of quinine methohydroxide. After standing for some hours at 0° the solution was evaporated to dryness at 25° in vacuo, thoroughly dried in high vacuum, and then triturated with ethyl acetate. The crystalline product was recrystallized from alcohol-ether (1:[illegible]) and obtained as clusters of fine colorless [illegible], m. p. 190–197°; $(\alpha)_D$ −118.5° (c, [illegible]% in MeOH); bacterial assay 101–[illegible]%; yield 1.20 g.

NOTES

Aromatic Aldehydes from Spruce and Maple Woods

By R. H. J. Creighton, Joseph L. McCarthy and Harold Hibbert

It has recently been reported[1] that a yield of 25% of vanillin based on Klason lignin can be obtained by treatment of spruce wood with alkali in the presence of nitrobenzene. Employing the same technique,[1] we have confirmed this result by digesting spruce woodmeal (25.0 g., 28.0% Klason lignin), sodium hydroxide solution (400 cc., 2 N), and nitrobenzene (24 cc.) in a stainless steel bomb with good agitation at 160° for three hours. In duplicate experiments, 1.73 and 2.12 g. of crude vanillin m-nitrobenzoylhydrazones (m. p. 204–209°) were finally isolated; after recrystallization, m. p. 210–211°; mixed m. p. 210–211°. Yields were 22.8 and 24.7%, respectively, calculated on the Klason lignin.

Application of this method to maple wood (38.5 g., 22.0% Klason lignin) left 13.7 g. of insoluble woody residue containing 0.2% Klason lignin. Neutralization of the alkaline reaction liquors and continuous extraction with benzene removed 4.23 g. of which 3.63 g. was extractable with sodium bisulfite solution. Acidification of the neutralized aqueous liquor to pH 3, and benzene extraction, yielded additional benzene-soluble substances (1.21 g.). The benzene-insoluble material precipitated by acidification of the alkaline aqueous reaction liquor weighed 4.1 g.

Vanillin and syringaldehyde were isolated from the bisulfite solution by acidification and benzene extraction. Their separation was effected by solution of the crude extract in 250 cc. of ethanol and fractional precipitation by gradual addition of increasing amounts of ammonia. In this way, by precipitation of the much more insoluble syringaldehyde addition product, crude syringaldehyde (2.7 g.) was isolated; m. p. 105–112°; after recrystallization, m. p. 110.5–112°; mixed m. p. gave no depression. The ammoniacal ethanol solution remaining after removal of the syringaldehyde component was evaporated to remove the ammonia and ethanol and the residue dissolved in about 125 cc. of dry ether. Addition of ammonia precipitated the crude addition product from which 0.55 g. of crude vanillin-containing material was isolated. A preliminary purification by sublimation[2] at 61° (1 mm.) yielded 0.29 g. crude vanillin (m. p. 75–80°) recrystallized m. p. 80–82°; mixed m. p. no depression. Vanillin was also isolated by direct fractional sublimation[2] of the bisulfite soluble material (3.56 g.) to yield 0.80 g. of crude vanillin (m. p. 77–81°). Precipitation of the total aldehydes in 3.03 g. of the bisulfite soluble extract yielded 7.01 g. of mixed m-nitrobenzoylhydrazones.

Based on the Klason lignin content of maple wood, the yield of syringaldehyde isolated by treatment with ammoniacal ethanol amounted to 31.8%; that of vanillin 3.4%. By sublimation 7.1% vanillin was obtained. By weight, the total yield of bisulfite soluble material was 42.9%, while the yield of total carbonyl-containing constituents of the bisulfite soluble fraction was [illegible].0% (calculated from the mixed m-nitrobenzoylhydrazones on the assumption of a syringaldehyde–vanillin ratio of 3:1). A duplicate experiment gave very similar yields.

(1) [illegible] and Hibbert, [illegible]

(2) [illegible] and [illegible], This Journal, [illegible], 2417 (1937).

Division of Industrial and Cellulose Chemistry
McGill University
Montreal, Canada Received November 18, 1940

α-Hydroxy-β,β-dimethyl-γ-butyrolactone

By Herbert E. Carter and Lyman F. Ney

In the course of work on analogs of pantothenic acid, it was discovered that α-hydroxy-β,β-dimethyl-γ-butyrolactone is obtained readily in a single step by treating an aqueous solution of α,α-dimethyl-β-hydroxypropionaldehyde with potassium cyanide and calcium chloride. The intermediate cyanohydrin is smoothly hydrolyzed at room temperature by the calcium hydroxide produced in the reaction.[1] Shortly after the completion of this work, Reichstein and Grüssner[2] reported a somewhat similar procedure for preparing the lactone. Since our method has certain

(1) This method has been used in the [illegible] by [illegible] [J. Chem. Soc., 419 (1938)] and by [illegible], 134 (1940)].

(2) Reichstein and Grüssner, Helv. Chim. Acta, 23, 650 (1940).

TABLE I

THE ABSORPTION (λ) OF THE METHYL AND CHLOROMETHYL DERIVATIVES (Log ε) OF THE SEVEN-RING ALKYL AND HALOGEN DERIVATIVES (Solvent: Ethanol)

Substituent	λ max.	Intensity
None	2705	1.88
	2865	1.99
	3005	1.96
	3125	1.06
	3265	1.06
	3505	1.89
	3680	2.90
5-Methyl	2740	1.95
	3040	1.96
	3225	1.08
	3330	1.05
	3550	1.94
	3745	2.84
5-Chloromethyl	2740	1.90
	2815	1.95
	3120	1.15
	3330	1.34
	3450	1.34
	3800	1.07
5,9-Dimethyl	(2500)	1.83
	2655	1.99
	2890	2.04
	2910	2.09
	3130	2.07
	3285	2.09
	3420	2.08
	3465	2.02
	3525	1.95
	3698	1.89

...bonyl group, similar to that of the unsubstituted hy...
...absorption curve from the usual ones for longer...
...have the fine structure of...
...Dimethylbenzanthracene differs somewhat from the...
...dimethyl derivatives, the most intense...
...somewhat lower resolution, while at longer...
...wavelengths the intensity of absorption is greater...
...for the maximum here.

The spectrum of 5-methylchrysene (I) is...
...peculiarity, interesting as in the 1,2-benzanthra...
...some cases such a bridge methylene group has...
...been observed to produce a considerable change...
...the spectrum, including an increase in the...
...amount of fine structure evident. This spectrum...
...of 5-methylchrysene also shows an increase...
...in the fine structure, particularly at...
...wavelengths comparable with 5-dimethylchrysene...
...(II), in the same position (Fig. 2). A...
...comparison between the dimethyl...
...and methylene derivatives is not possible in the...

UNITED STATES PATENT OFFICE

2,234,680

PROCESS OF PREPARING PANTOTHENIC ACID

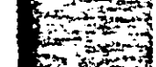
Marjorie B. Moore, Highland Park, and Karl Folkers, Chicago, Ill., assignors to Abbott Laboratories, North Chicago, Ill., a corporation of Illinois

No Drawing. Application July 22, 1938, Serial No. 220,497

Claims. (Cl. 260—534)

The present invention relates to the process of preparing a complex organic acid known as the d- as pantothenic acid.

d-Pantothenic acid, a member of the class of β-alanine, may be represented by the following formula:



and its synthesis due to its complex structure has presented many difficulties, the presence of various type reactive groups in the molecule, for example, makes the use of acid chlorides extremely difficult and as a result the synthesis of the acid particularly in a satisfactory form for use in the therapeutic field has presented the art with the problem of process of preparation.

The principal object of the present invention is to provide the art with a satisfactory process for the preparation of pantothenic acid resulting in the synthesis of the acid in the desired form for therapeutic use.

Other objects of the present invention will be apparent as the description proceeds.

I have discovered after an extensive research investigation that pantothenic acid may be prepared in the desired form by reacting (i. e. fusing) β-alanine (β-amino-propionic acid) with a member selected from the group consisting of α,γ-dihydroxy-β,β-dimethyl-α-butyric acid and α,γ-dihydroxy-β,β-dimethyl-butyro-γ-lactone. This method (employing the specified lactone) has demonstrated that it is from the economical point of view, practicable and presents in a yield of final product, exceptionally suited for use in the therapeutic field. The following example will serve for illustrative purposes:

Example

About 220 grams (1 mole) of α,γ-dihydroxy-β,β-dimethyl-butyro-γ-lactone and about 89 grams (1 mole) of β-alanine are mixed and gradually heated with occasional stirring, up to about 178° C. crystals of β-alanine are present and there is no sign of chemical reaction. Around this temperature (i. e. 178° C.) however, the mixture begins to bubble vigorously indicating that a chemical reaction is under way.

The temperature of the reaction mixture is ordinarily maintained at, or preferably above, 178° C. for about 15 minutes or longer to complete the reaction indicated by no further bubbling. The final liquid reaction product which is almost colorless and does not deposit crystals if it remains substantially free from solid material when cooled, may be used directly in the form obtained for further treatment or purification if necessary. If desired the final acid product may be converted to form salts e. g. calcium pantothenate, and be administered in such form.

It will be understood that the present invention is not limited to the above illustrative example. Various modifications of the present invention are intended to be covered by the following claims.

I claim:

1. The process of preparing pantothenic acid, the vitamin B complex which comprises fusing a mixture made up of β-alanine and a member selected from the group consisting of α,γ-dihydroxy-β,β-dimethyl-α-butyric acid and α,γ-dihydroxy-β,β-dimethyl-butyro-γ-lactone.

2. The process of preparing pantothenic acid, the vitamin B complex which comprises fusing a mixture made up of about molecular proportions of α,γ-dihydroxy-β,β-dimethyl-butyro-γ-lactone and β-amino-propionic acid to a temperature of about 178° C. until complete fusion occurs and the resulting liquid reaction product is substantially free from solid material on cooling.

MARJORIE B. MOORE.

halten. Nach 2 Tagen destilliert man bis auf 10 cm ab und saugt die beim Erkalten ausgeschiedenen Krystalle ab; Ausbeute 2,4 g. Das Mutterlauge wird nach Zusatz von 20 cm³ Wasser auf dem Wasserbad auf die Hälfte eingedampft und gibt beim Erkalten 1,4 g weitere Krystalle, die nach Umlösen aus der 25-fachen Menge Alkohol bei 125° schmelzen. Das vereinigte Krystallisat (3,4 g) erweist sich nach Umkrystallisieren als identisch, enthält aber kleine Mengen höherschmelzender Anteile. Sehr leicht in Chloroform und warmem Wasser, weniger in Alkohol.

3,240 mg Substanz gaben 4,030 mg CO_2 und 0,965 mg H_2O

$C_{14}H_{17}O_4N_3Cl_2$ Ber. C 34,01 H 3,47%

Gef. „ 33,59 „ 3,33%

40) Monatl. Beweis. Chlorierung von 2 g reinem Gemisches von 2- und 3-Diäthylaminotilbenol mit 0,7 g Sulfurylchlorid in Chloroform bei Raumtemperatur.

4,800 mg Substanz gaben 7,240 mg CO_2 und 1,165 mg H_2O

$C_{14}H_{17}O_4N_3Cl_2$ Ber. C 41,77 H 4,26%

Gef. „ 41,50 „ 4,27%

41) Monatl. Beweis. Chlorierung von 0,5 g 5-Form-2-phenylindol mit 0,3 g Sulfurylchlorid in Chloroform bei Raumtemperatur; Ausbeute 0,2 g der Theorie.

Universität Basel, Anstalt für Organische Chemie.

21. Krystallisiertes Natriumsalz der Pantothensäure

von P. Karrer, Richter, H. Reich und T. Reichstein.

(8. II. 41.)

Die von *R. J. Williams* und Mitarbeitern entdeckte Pantothensäure[1]) besitzt erhebliche biologische Bedeutung. Sie wird von vielen Einzellern sowie von höheren Tieren benötigt, und es ist sehr wahrscheinlich, dass sie auch für den Menschen die Rolle eines Vitamins spielt. Sowohl für tierexperimentelle wie für chemische Versuche wäre es daher zweckmässig, einen brauchbaren Standard mit genau bekanntem Gehalt an Pantothensäure zu besitzen. Die freie Säure ist für diesen Zweck wenig geeignet, da sie flüssig ist und nicht krystallisiert, weshalb man keine sicheren Kriterien für ihre Reinheit besitzt. Von Salzen sind bisher lediglich das Chininsalz[2]) sowie das Benzylchinoniumsalz[3]) in krystallisierter Form beschrieben worden. Beide sind für biologische Versuche wenig geeignet. Auf der Suche nach

[1]) R. J. Williams, vgl. diese Arbeit, erschienene Sammelreferate von R. J. Williams, E. Baker, E. E. Snell, E. Wright, Physiological Reviews 21, 69 (1941).

[2]) R. J. Williams, E. H. Rohrman, E. M. Lyman, J. Am. Chem. Soc. 62, 1124 (1940).

[3]) Chr. Subbarow, J. Biol. Chem. 136, 797 (1940); C. A. 34, 1765 (1940). Diese Forscher beschreiben auch das Benzylchinoniumsalz der [illegible] Säure, die durch [illegible] gewonnen wurde. Auch das entsprechende Salz der [illegible] Säure [illegible] (durch [illegible]). Schmp. [illegible] Zersetzung.

einem krystallisierten Derivat, das auch für klinische Anwendung am Menschen verwendbar ist, fanden wir im Natriumsalz den bisher aus sichtsreichsten Vertreter. Dieses Salz lässt sich leicht bereiten und krystallisiert aus Alkohol unter Zusatz von Aceton oder Äther in gut ausgebildeten, farblosen Nädelchen, die bei 121—122° unzersetzt schmelzen und eine spez. Drehung von $[\alpha]_D^{20}$ = +29° ± 1,5° (Wasser) besitzen. Das Natriumsalz hat auch den Vorteil, für Injektionszwecke besonders brauchbar zu sein, da Natrium bekanntlich von allen Ionen bei dieser Anwendungsart am besten verträglich ist. Der grösste Nachteil dieses Salzes ist der, dass es sehr hygroskopisch ist und an feuchter Luft bereits nach wenigen Minuten zerfliesst. Es muss somit entweder im Exsikkator oder in luftdicht verschlossenen, am besten verschmolzenen Ampullen aufbewahrt werden. Trotzdem scheint es uns, aus den eingangs genannten Gründen, als Standardsubstanz für biologische Versuche gegenüber allen anderen bisher bekannten Derivaten der Pantothensäure den grössten Vorzug zu besitzen.

Das Natriumsalz wurde aufgenommen von destilliertem, analysenreinem d(+)-Pantothensäure-äthylester[2]) bereitet, der durch vorsichtige Verseifung mit der berechneten Menge Bariumhydroxyd ins Bariumsalz übergeführt wurde. Das Bariumsalz wurde dann mit Natriumsulfat umgesetzt. Das Natriumsalz ist ausserdem in einfacherer Weise direkt durch Erwärmen von d(−)-Oxy-β,β-dimethyl-butyrolacton mit trockenem β-Alaninnatrium erhältlich[3]). Am bequemsten wird diese Reaktion so ausgeführt, dass man β-Alanin in der äquimolaren Menge einer trockenen Natriummethylatlösung auflöst und das Lacton zusetzt. Nach 1—2-tägigem Stehen bei Zimmertemperatur ist die Umsetzung beendet, und es werden Ausbeuten von etwa 90% der Theorie an krystallisiertem Natriumsalz erhalten.

[illegible] Gedanken der Firma [illegible] Material.

Experimenteller Teil.

d(+)-Pantothensaures Natrium.

2,3 g d(+)-Pantothensäure-Barium (aus destilliertem Äthylester gewonnen[2]) wurden in 25 cm³ Wasser gelöst und bei 60° möglichst genau mit einer 2-n. Natriumsulfatlösung von derselben Temperatur gefällt. Hierzu wurden etwa 0,57 g wasserfreies Natriumsulfat benötigt. Dann wurde sofort abgekühlt, das Bariumsulfat durch Zentrifugieren entfernt und die klare Lösung im Vakuum

[illegible] Helv. 23, 778 (1940).

[illegible] Helv. 23, 850 (1940).

[illegible] Am. Soc. 62, 1628 (1940).

[illegible] 784 (1940).

eingedampft. Der verbleibende Sirup kristallisierte nach mehrtägigem Stehen im Vakuum-Exsikkator über Calciumchlorid. Nach Entnahme von etwas Impfmaterial wurde in wenig absolutem Alkohol gelöst und die leicht trübe Lösung über einer Spur Kohle blank filtriert und unter Umschwenken mit Aceton bis knapp zum Auftreten einer bleibenden Trübung versetzt, die durch Zusatz von einem Tropfen Alkohol wieder entfernt wurde. Beim Animpfen trat bald reichliche Kristallisation ein, die durch vorsichtigen Acetonzusatz allmählich möglichst vervollständigt wurde. Die Kristalle wurden abgenutscht, mit Alkohol-Aceton (1 : 1), dann (1 : 2), anschliessend mit reinem Aceton und zuletzt mit Äther gewaschen und im Vakuum über Calciumchlorid getrocknet. Sie schmolzen bei 120—122°. Nochmaliges Umkristallisieren aus Alkohol-Aceton gab farblose, verfilzte Nadeln, die bei 121—122° korr. unzersetzt schmolzen. Die spez. Drehung betrug: $[\alpha]_D^{20} = -29{,}5° \pm 1{,}5°$ (c = 1,9 in Wasser).

4,7 mg Subst. (2½ Stunden bei 0,025 mm und Zimmertemperatur getrocknet) ... 9,02 mg CO_2, ... mg H_2O (korr.) ... 0,02%

Zur Analyse wurde 1 Stunde bei 0,03 mm und 60° getrocknet.

$C_{11}H_{20}O_6NNa$ (301,23) Ber. C 44,81 H 6,89 ... 0,53%

Gef. „ 44,24 „ 6,94 ... 0,57%

Das zweimal umkristallisierte Präparat war merklich weniger hygroskopisch als das nur einmal umkristallisierte. An feuchter Luft verfliesst es jedoch auch sehr bald.

Ein identisches Produkt wurde in einer Ausbeute von 39% der Theorie aus folgendem Ansatz erhalten: 1,76 g trockenes β-Alanin wurden unter leichtem Wärmen in 20 cm³ einer trockenen Natriummethylat-Lösung gelöst, die 0,46 g Natrium enthielt. Nach dem Erkalten wurden 2,6 g dl-(α)-Oxy-β,β-dimethyl-butyrolacton zugegeben und die Mischung zwei Tage bei Zimmertemperatur stehen gelassen. Nach dem Eindampfen im Vakuum wurde der gut getrocknete Rückstand aus Alkohol-Aceton wie oben umkristallisiert.

dl-(α)-Pantothensaures Natrium:

Das Natriumsalz der dl-(α)-Pantothensäure wurde in kleiner Menge genau wie oben aus dem Bariumsalz bereitet. Es schmolz nach nur einmaligem Umkristallisieren bei 120—122° und zeigte eine spez. Drehung von: $[\alpha]_D^{20} = -27{,}1° \pm 2{,}5°$ (c = 0,875 in Wasser).

4,863 mg Subst. (2 Stunden im Hochvakuum bei Zimmertemperatur getrocknet) ... 10,25 mg CO_2, ... mg H_2O (korr.) ... 0,21% ...

Die Analysen wurden im mikrochemischen Laboratorium der Firma Dr. Hoffmann-La Roche & Co., Basel, ausgeführt.

Pharmazeutische Anstalt der Universität Basel.

145. Krystallisierte Chininsalze der (+)- und (−)-Pantothensäure und die biologische Wirksamkeit des (+)-Pantothensäure-äthylesters

von R. Grössner, W. Kittel, R. Richter und T. Reichstein.

(12. IX. 40.)

Vor kurzem beschrieben wir ein einfaches Verfahren zur Herstellung der β-Alanide von Oxysäuren[1]), welches darauf beruht, dass man Oxylactone mit Estern, Salzen oder Amiden des β-Alanins umsetzt und das insbesondere auch zur Herstellung von Pantothensäure sehr geeignet ist. In verschiedenen, vor kurzem erschienenen Mitteilungen von *Babcock* und *Wake*[2]), *Williams* und Mitarbeitern[3]), *Stiller* und Mitarbeitern[4]) ist zur Synthese der Pantothensäure und verwandter Stoffe dasselbe Verfahren als besonders geeignet befunden worden. Auch der dort[4]) zur Gewinnung der optisch aktiven Formen beschrittene Weg ist mit dem von uns benutzten fast bis in alle Einzelheiten identisch, so wurde die Spaltung der (±)-Dioxy-3,3-dimethylbuttersäure (I) an die optischen Antipoden auch über die Chininsalze erreicht. Dies ist kein Zufall, denn von allen leicht zugänglichen Alkaloiden ist für diesen Zweck nur Chinin gut geeignet.

In unserer letzten Mitteilung wurde nur die Bereitung des reinen (+)-Pantothensäure-esters beschrieben, wobei einschränkend erwähnt wurde, dass noch weitere Versuche vorgesehen seien, ob bei der Bereitung keine partielle Racemisierung eingetreten ist. Es zeigte sich, dass es sich wirklich um die optisch reine Form gehandelt hat. Inzwischen wurde auch der biologisch unwirksame (−)-Pantothensäure-ester bereitet. Da dieser aber gelegentlich auch von den Amerikanern[2]) beschrieben wurde, so sollen nur diejenigen Punkte erwähnt werden, die eine Ergänzung darstellen.

Während das zur Bereitung der (+)-Säure als Ausgangsmaterial benötigte (+)-Lacton (II) aus dem schwerlöslichen Chininsalz sofort in optisch reiner Form erhalten wird, ist das aus dem leichtlöslichen Chininsalz erhältliche (−)-Lacton (III) naturgemäss immer mit etwas Racemat verunreinigt (*Stiller* und Mitarbeiter[4]) gewannen es

[1]) R. Grössner, W. Kittel, R. Richter und T. Reichstein, Helv. 23, 850 (1940).

[2]) J. K. Babcock, J. C. Keresztesy, H. R. Sullivan, C. H. Shunk, E. L. Wittle, R. Duggan, J. H. Williams, Am. Soc. 62, 1683 (1940).

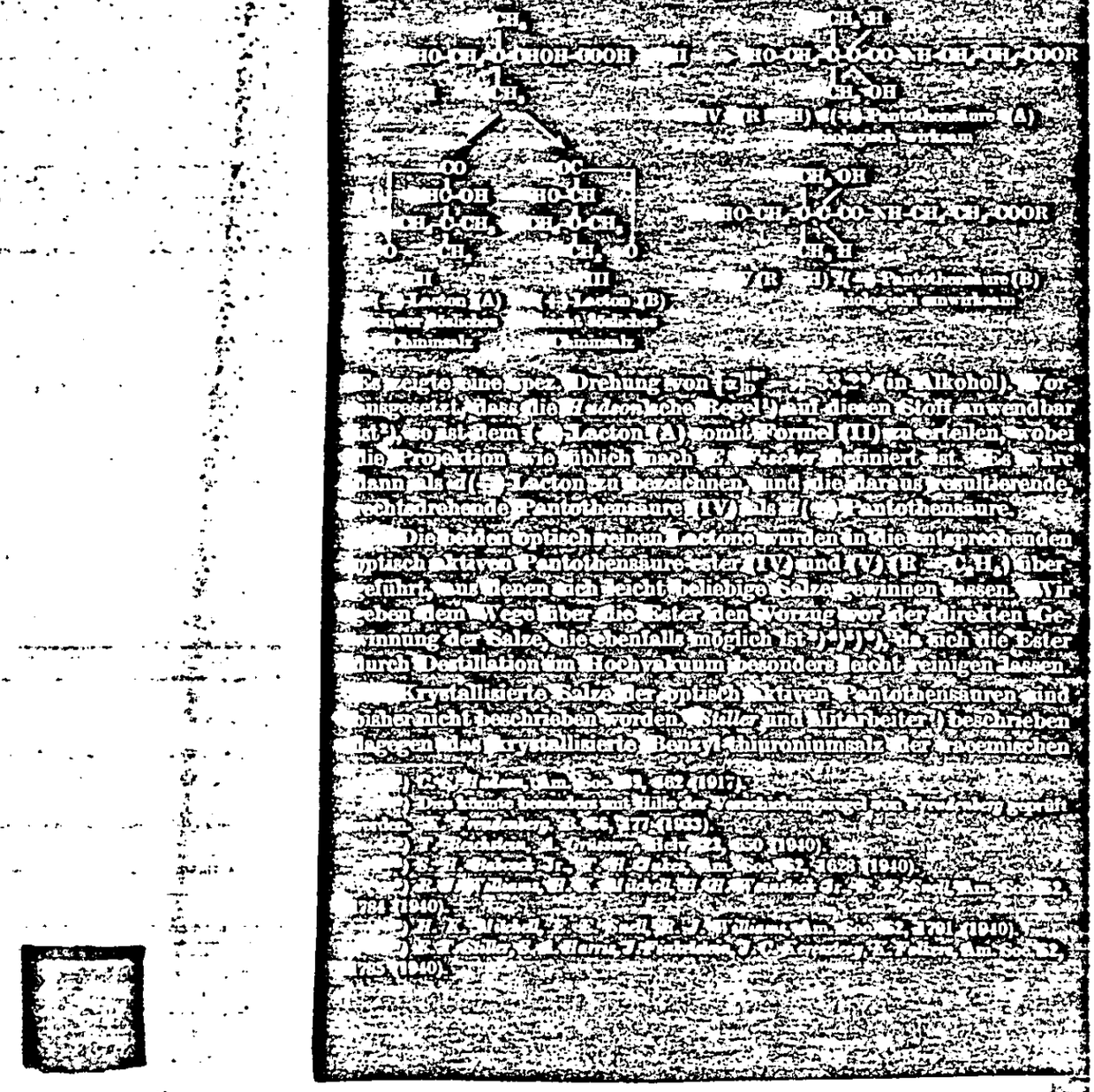
[3]) H. R. Wake, W. H. Peterson, C. H. Shunk, E. L. Wittle, J. H. Williams, Am. Soc. 62, 1776 (1940).

[4]) E. T. Stiller, J. C. Keresztesy, J. H. Williams, Am. Soc. 62, 1784 (1940).

[5]) H. R. Wake, J. H. Williams, Am. Soc. 62, 1791 (1940).

[6]) E. T. Stiller, J. C. Keresztesy, J. H. Williams, Am. Soc. 62, 1863 (1940).

einfach durch Umkristallisieren des über das leichtlösliche Chininsalz angereicherten Produktes. Wir fanden, dass auch das Bariumsalz für die Reinigung gut brauchbar ist. Zur Abklärung, welche der beiden Formeln (II) oder (III) den beiden Lactonen zuzuordnen sind, haben wir das γ-Lacton ins Phenylhydrazid verwandelt. Dieses ist ölig, liess sich aber durch Destillation im Hochvakuum reinigen.



Es zeigte eine spez. Drehung von $[\alpha]_D^{20} = -33{,}2°$ (in Alkohol). Vorausgesetzt, dass die *Hudson*sche Regel[1]) auf diesen Stoff anwendbar ist[2]), so ist dem (−)-Lacton (A) somit Formel (II) zu erteilen, wobei die Projektion wie üblich nach *E. Fischer* orientiert ist. Wir wären demnach z.Z. (−)-Lactone zu bezeichnen, und die daraus resultierende rechtsdrehende Pantothensäure (IV) als d(+)-Pantothensäure.

Die beiden optisch reinen Lactone wurden in die entsprechenden optisch aktiven Pantothensäure-ester (IV) und (V) (R = C_2H_5) überführt, aus denen sich leicht beliebige Salze gewinnen lassen. Wir geben dem Wege über die Ester den Vorzug vor der direkten Gewinnung der Salze, die ebenfalls möglich ist[3]), da sich die Ester durch Destillation im Hochvakuum besonders leicht reinigen lassen.

Krystallisierte Salze der optisch aktiven Pantothensäuren sind bisher nicht beschrieben worden. *Staiger* und Mitarbeiter[4]) beschrieben allerdings das krystallisierte Benzyl-thiuroniumsalz der racemischen

[1]) C. S. Hudson, Am. Soc. 31, 482 (1917).
[2]) Eine kürzlich von Klyne [Biochemical Journal 38, 395 (1944)] mitgeteilte Anwendung der Regel auf Lactone mit 5 Ringgliedern ist nicht einwandfrei. Siehe dazu auch: K. Freudenberg, Chem. Ber. 77, 177 (1944).
[3]) R. Kuhn, H. Trischmann, Helv. 23, 450 (1940).
[4]) R. J. Stedman, L. Hays, J. Org. Chem. Am. Soc. 22, 1628 (1940).
[5]) R. J. Williams, R. B. Wilson, J. Am. Chem. Soc. 62, 1784 (1940).
[6]) R. J. Williams, J. H. Truesdail, J. Am. Chem. Soc. 62, 1785 (1940).
[7]) R. J. Stedman, L. Hays, J. Org. Chem. Am. Soc. 22, 1785 (1940).

Pantothensäure. Barium- und Calciumsalze, die auch durch Umfällung gereinigt wurden, sind zwar nach Angaben der genannten Autoren mikrokristallin (anisotrop), bieten jedoch keine Gewähr für Reinheit, da sie auch nicht in deutlich ausgebildeten Krystallen erhalten wurden. Auf der Suche nach eindeutig krystallisierbaren Salzen fanden wir im Chinin wieder eine geeignete Base. Mit beiden optisch aktiven Pantothensäuren werden krystallisierte Salze erhalten, die sich in ihrer Löslichkeit, besonders in Aceton sehr stark unterscheiden, so dass auch racemische Pantothensäure mit Hilfe von Chinin in die optisch aktiven Formen gespalten werden kann. Das Chininsalz der biologisch wirksamen (+)-Pantothensäure (IV) (R = H) ist in Aceton relativ gut löslich und krystallisiert aus heissem Aceton in farblosen Nadeln vom Smp. 136° korr., die 1 Mol Wasser enthalten, das sich schwer ganz vertreiben lässt. Es besitzt die spezifische Drehung $[\alpha]_D^{20}$ = −95° (in Wasser). Das Chininsalz der biologisch unwirksamen (−)-Pantothensäure ist auch in heissem Aceton sehr schwer löslich. Es krystallisiert aus Alkohol in äusserst feinen, filzigen Nädelchen, die bei 183,5° schmelzen und zeigt die spez. Drehung von $[\alpha]_D^{20}$ = +21° (in Wasser).

Auch die Natriumsalze der beiden optisch aktiven Pantothensäuren sind inzwischen krystallinisch erhalten worden, doch handelt es sich um äusserst hygroskopische Substanzen, so dass noch keine genaueren Bestimmungen gemacht werden konnten.

Bezüglich der biologischen Prüfung an Ratten liegen eindeutige Resultate über die Wirkung der zwei optisch aktiven Pantothensäure-äthylester vor, über die der folgende Bericht aus dem pharmakologischen Laboratorium der *A. Hoffmann-La Roche & Co. A.G.*, Basel, orientiert.

Der (+)-Pantothensäure-ester (IV, R = H) erweist sich in Dosen von 10 γ pro Tag an der Ratte als stark wirksam. Die Gewichtszunahme betrug im Durchschnitt 1,5 g pro Tag, während die Kontrolltiere 0,3 g pro Tag zunahmen. Mit 50 γ (+)-Pantothensäure-ester pro Tag war der tägliche Gewichtsanstieg noch etwas ausgeprägter als mit 10 γ, er betrug 1,9 g. Auch bei Zufuhr sehr viel grösserer Mengen (+)-Pantothensäure-ester, nämlich 1,5 mg, konnte keine grössere Gewichtszunahme erzielt werden. Mit 300 γ racemischem Pantothensäure-methylester wurde eine Gewichtszunahme von 2,3 g, mit 30 γ eine solche von 2,1 g pro Tag erreicht. Die Kontrolltiere nahmen bei diesem Versuch etwas stärker, nämlich um 0,7 g täglich zu; die Gewichtsdifferenz zwischen den mit racemischem Pantothensäure-ester gefütterten Tieren und den Kontrollen ist also gleich gross wie bei den Versuchen mit (+)-Pantothensäure-ester.

[illegible] (1940).

Der tägliche Bedarf der Ratte an d(+)-Pantothensäure dürfte bei etwa 10 γ liegen.

Im Gegensatz zum d(+)-Pantothensäure-ester erwies sich der d(−)-Ester in Dosen von 10 γ als ganz unwirksam (s. Kurvenbild S. 1280), in solchen von 50 γ als kaum wirksam. Dies bestätigt die Resultate der amerikanischen Forscher[1]) und ergänzt sie insofern, als auch an Ratten nicht nur die freie d(+)-Säure und ihre Salze, sondern auch die Ester als wirksam erweisen.

Das racemische Lacton (II) bewirkte an Ratten, die gleichzeitig d-Alanin erhielten, in Dosen von 3 mg pro Tag eine Gewichtszunahme von durchschnittlich 1,2 g täglich, während die Kontrolltiere eine solche von 0,42 g aufwiesen. In einer anderen Versuchsreihe wurde durch tägliche Zulage von 0,5 mg d(+)-Lacton ein Gewichtsanstieg von 1,8 g pro Tag erzielt.

Bemerkenswert ist, dass ausser der Gewichtszunahme auch eine deutliche Vermehrung der Reticulocytenzahlen in den ersten Tagen nach der Pantothensäure-Zufuhr beobachtet wurde. Zur Feststellung, ob es sich dabei um eine spezifische Wirkung der Pantothensäure handelt, sind noch weitere Versuche notwendig. Es wurde auch bei Zufuhr anderer Vitamine eine Zunahme der Reticulocyten festgestellt. So haben *Ferranini* und *Murador*[2]) nach Zufuhr von 5 mg Nicotinsäure an 100 g schweren Ratten erhöhte Reticulocytenzahlen gefunden. *Euler* und *Malmberg*[3]) haben nach Verabreichung von Ascorbinsäure die gleiche Beobachtung gemacht.

Von Bedeutung wären klinische Versuche darüber, ob auch gewisse Anämien mit Pantothensäure günstig beeinflussen lassen.

Biologische Prüfung der Pantothensäure

Zur biologischen Prüfung der Pantothensäure-Präparate wurde einerseits der Ratten-Wachstumstest, anderseits die Bestimmung der Reticulocytenzahlen herangezogen.

Als Versuchstiere dienten Ratten eigener Zucht (Glanzkopf) verschiedenen Geschlechts im Alter von 25 Tagen und darüber. Sie wurden nach dieser Zeit ein Gewicht von 50—60 g und zur Vorbereitung für die Versuche während der ersten Tage nach dem Entritt ausschliesslich mit einer Grundkost [illegible]

[1]) *H. K. Mitchell, E. E. Snell* und *R. J. Williams*, J. Am. Soc. **62**, 1776 (1940).

[2]) *L. Ferranini* und *G. Murador*, Arch. Sc. biol. **26**, 384 (1940).

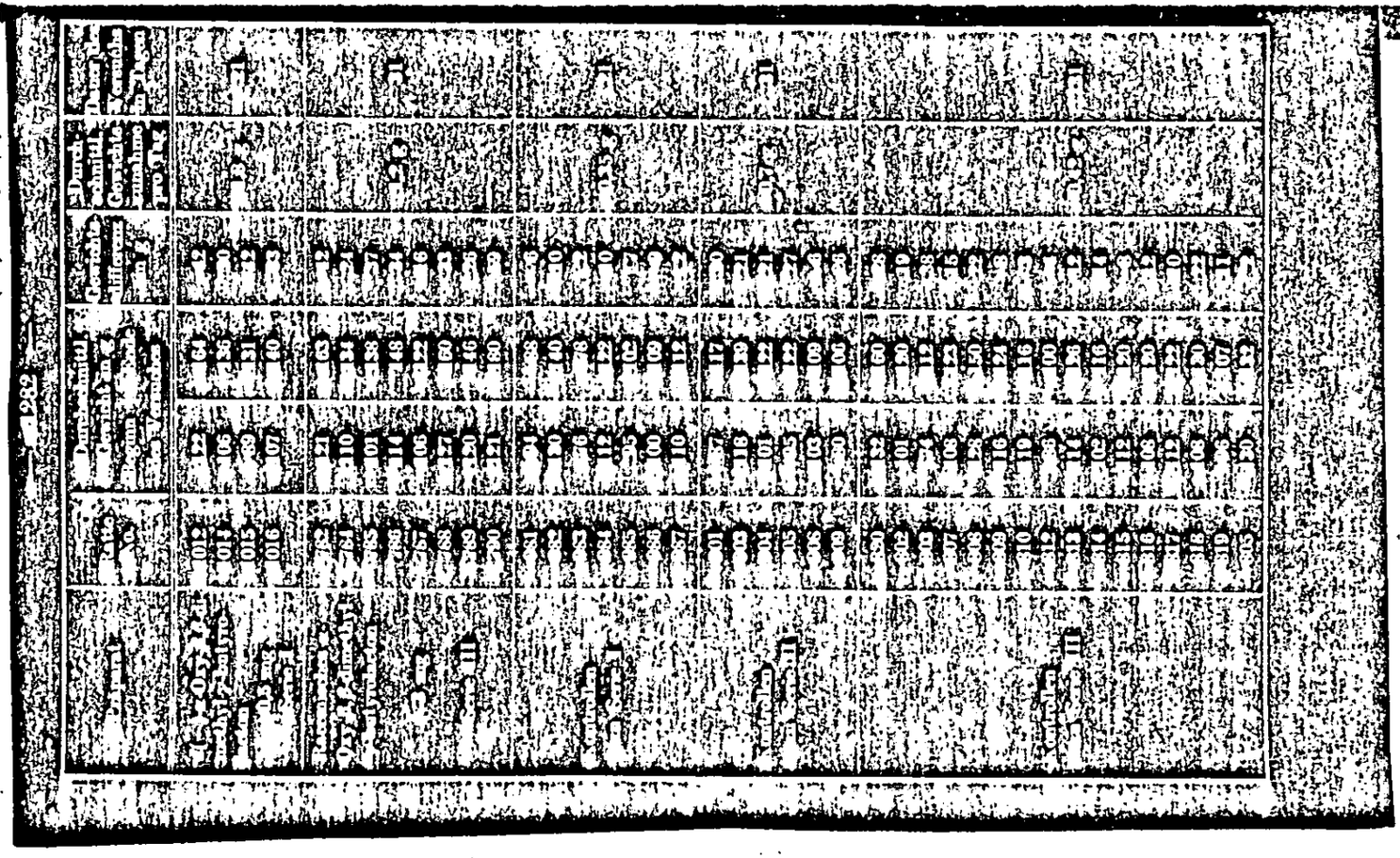
[3]) *H. v. Euler* und *G. Malmberg*, Z. physiol. Chem. **265**, 285 (1940).

[4]) *H. Boll*, Arch. Exp. Path. **194**, 376 (1939).

[5]) *Z. Ayyad*, Diss. Bern (1939).

In folgenden Tabellen sind die Versuchsergebnisse zusammengestellt.

Tiergruppe	Tiernummer	Durchschnittl. Gewicht in g: Anfang	Ende	Gewichtsdifferenz in g	Durchschnittl. Gewichtszunahme pro Tag	Dauer der Versuche in Tagen
(B.) Kontrollen	988	133	165	32		
	989	98	138	40		
	990	115	155	40	1.5 g	21
0.7	991	96	107	11		
	995	79	101	22		
	996	110	151	41		
	997	92	106	14		
0.7	998	106	140	34	1.9 g	21
	999	122	167	45		
1	1000	96	110	15		
(B.) Kontrollen	926	115	179	64		
	928	91	145	54		
	927	102	153	51		
3	928	98	155	57	2.5 g	21
	929	100	154	54		
7	930	102	155	53		
(B.) Kontrollen	1001	115	128	13		
	1002	94	132	38		
	1003	100	108	8	0.5 g	21
0.7	1004	118	120	2		
	1005	92	100	8		
	1006	110	117	7		
	1007	100	108	8		
0.7	1008	87	110	23	1.5 g	21
	1009	127	148	21		
1	1010	93	110	16		
	816	90	161	71		
	817	93	165	72		
	818	92	177	85	2.8 g	21
3	819	122	199	77		
	820	99	172	73		
	821	98	136	38		
	822	100	165	65		
0.7	823	96	171	75	2.1 g	21
	824	90	156	66		
7	825	75	140	65		



Reticulocyten. Die Bestimmung der Reticulocyten erfolgte nach der Vitalfärbemethode unter Verwendung von Brillant-Cresylblau, welches die Reticulocyten intensiv dunkelblau anfärbt, während die Erythrocyten homogen hellgrün erscheinen. Die Blutentnahme erfolgte in allen Fällen gegen 10 Uhr, die Verarbeitung der Präparate binnen 1–2, bzw. 3 Tagen nach deren Verbreitung. In jedem Ausstrich wurden die auf 1000 Erythrocyten entfallenden Reticulocyten gezählt. Die Schwankungen zwischen den einzelnen Tieren einer Versuchsreihe sind sehr erheblich, so wurden bei den Kontrollen eigene Reticulocytenzahlen von 0,4 – 3,4 % gefunden. Es erwies sich somit die Notwendigkeit, vom statistischen an einer grossen Zahl von Kontrolltieren, bzw. mit Pantothensäure gefütterten Tieren, die Reticulocytenwerte zu verfolgen. Ratten, die vom Vitamin B-Komplex Thiamin, Pantothensäure, Adermin, Inosin und Cholin und Cholinhaltige erhalten, waren im Alter von 2–3 Monaten durchschnittlich einen Gehalt von 1,5 % Reticulocyten auf. Dieser Durchschnittswert wurde durch Blutuntersuchungen an über 100 Tieren ermittelt. Nach Zufuhr verschiedener Dosen von (+)-Pantothensäure (siehe Abschn. die oben beschriebenen Wachstumsversuche) wurden Reticulocytenwerte von durchschnittlich 3,4 % gefunden. Die Zahl stellt den Durchschnitt von 30 Versuchstieren der beim günstigsten Fall beobachteten Vermehrung von (+)-Pantothensäure zum Reticulocytenanstieg von 1,4 auf 3,2 % beobachtet wurden.

Experimenteller Teil.

Herstellung der reinen dl-(+)- und d-(+)-α-Oxy-β,β-dimethylbutyrolactone (II) und (III).

20 g dl-α-Oxy-β,β-dimethyl-butyrolacton wurden in 50 ccm Methanol gelöst und ½ Stunde mit der Lösung von 27 g krystallisiertem Bariumhydroxyd in 500 ccm Methanol unter Rückfluss gekocht. Dann wurde mit Kohlendioxyd neutralisiert und vom Bariumcarbonat abfiltriert. Das Filtrat wurde mit der heissen Lösung von Chininsulfat in Methanol genau ausgefällt, wozu etwa 80 g Chininsulfat in 800 ccm Methanol nötig waren. Das Bariumsulfat wurde durch Zentrifugieren entfernt. Die Lösung gab beim Einengen zunächst 30 g rohes, schwerlösliches Chininsalz (A). Aus den Mutterlaugen wurden, wie früher beschrieben, 28 g rohes Chininsalz (B) erhalten. Aus den ersteren wurden durch Umkrystallisieren aus Methanol 26 g reines A-Salz gewonnen. Das rohe B-Salz wurde aus Methanol-Äther umkrystallisiert und gab 23 g vereinigtes B-Salz.

Zur Spaltung wurden 26 g A-Salz in 500 ccm Methanol gelöst, mit der Lösung von 11 g Bariumhydroxyd in heissem Wasser versetzt und im Vakuum vom Methanol befreit. Dem Rückstand wurde durch Ausschütteln mit Chloroform das Chinin entzogen und Chloroform durch Ausschütteln mit Äther entfernt. Dann wurde mit Kohlendioxyd neutralisiert, vom Bariumcarbonat abfiltriert und die klare Lösung eingedampft. Der Rückstand wurde aus wenig Wasser durch Zusatz von Aceton umkrystallisiert und gab 10,5 g reines Bariumsalz (A), vom Smp. 198–200° (Zers.). Es zeigte eine spez. Drehung von $[\alpha]_D^{20} = +3,0°$ ± 0,5° (c = 2,31 in Wasser).

Die 23 g Chininsalz (B) wurden analog mit Bariumhydroxyd gespalten. Das rohe Bariumsalz (10 g) wurde in 10 ccm Wasser gelöst und mit 30 ccm Aceton versetzt, wobei sich Krystall-

Nadeln aus, die abgenutscht und mit Methanol gewaschen wurden. Sie wogen 4,3 g und schmolzen nach einmaligem Umkrystallisieren aus Wasser mit Alkohol bei 220° korr. (Zers.). Es handelt sich um das chemische Bariumsalz. Dasselbe Salz wird nämlich erhalten, wenn gleiche Gewichtsmengen des (+)- und (−)-Salzes in Methanol gelöst, zusammengegeben und mit einer Spur Wasser versetzt werden. Zur Analyse wurde an der Luft getrocknet.

4,518 mg Subst. in 1 ccm Lösung: α_D = 0,86°

$C_{14}H_{18}O_6Ba$ Ber. Ba 31,8 Gef. Ba 32,0%

Die Mutterlauge der genannten Krystalle wurde mit Aceton bis fast zur Trübung versetzt und angeimpft, wobei sofort Krystallisation einsetzte, die durch längeres Stehen bei 0° und vorsichtigen Zusatz von Aceton möglichst vervollständigt wurde. Erhalten wurden 4,2 g Bariumsalz (B), das nach einmaligem Umkrystallisieren aus Wasser/Aceton bei 198—200° korr. (Zers.) schmolz. Die spez. Drehung betrug $[\alpha]_D$ = −0,5° ± 5,0° (c = 3,15 in Wasser).

Zur Gewinnung des freien Lactons wurden 10 g Bariumsalz (A) in absolutem Alkohol gelöst und mit etwas mehr als der berechneten Menge alkoholischer Salzsäure versetzt. Das ausfallende Bariumchlorid wurde abfiltriert, das Filtrat im Vakuum eingedampft und der Rückstand durch zweimaliges Abdampfen mit etwas Benzol getrocknet. Der krystallisierte Rückstand wurde im Hochvakuum sublimiert. Das farblose, krystallisierte Sublimat schmolz roh bei 87—89° und zeigte eine spez. Drehung von $[\alpha]_D$ = −1,6° ± 0,5° (c = 6,25 in Aceton). Einmaliges Umkrystallisieren aus Benzol-Petroläther brachte den Smp. auf 89—90°. Die spez. Drehung betrug $[\alpha]_D$ = −1,4° ± 0,5° (c = 3,813 in Aceton) bzw. $[\alpha]_D$ = −1,9° ± 0,5° (c = 1,012 in Wasser).

Analog wurde das Bariumsalz (B) in freies (+)-Lacton (II) übergeführt. Das farblose Sublimat des Rohproduktes zeigte einen Smp. von 87—89° und eine spez. Drehung von $[\alpha]_D$ = +1,1° ± 1° (c = 1,98 in Aceton). Einmaliges Umkrystallisieren aus Benzol-Petroläther ergab farblose Nadeln vom Smp. 89—90°. Die spez. Drehung betrug $[\alpha]_D$ = +1,3° ± 0,5° (c = 3,91 in Aceton) bzw. $[\alpha]_D$ = +1,3° ± 0,5° (c = 1,31 in Wasser).

Phenylhydrazid der 4-(2,6-Dioxy-3,5-dimethyl-phenyl)-buttersäure

50 mg (+)-Lacton (II) und 50 mg reines Phenylhydrazin wurden in Kohlendioxyd-Atmosphäre ½ Stunde auf 100° erwärmt. Im Molekülkolben wurde bei 10° Badtemperatur ein geringer Vorlauf abgetrennt, dann destillierte unter 0,01 mm das Phenylhydrazid als farbloses Öl bei 185° Badtemperatur. Es konnte nicht zum Krystallisieren gebracht werden und zeigte eine spez. Drehung von $[\alpha]_D$ = +3,2° ± 1° (c = 3,9 in Alkohol).

(+)-Pantothensäure-äthylester (IV, R = C_2H_5).

1 g (+)-Lacton (A) (II) und 0,9 g frisch im Vakuum destillierter β-Alanin-äthylester wurden in 5 ccm absolutem Alkohol 1 Stunde auf dem siedenden Wasserbad erhitzt. Dann wurde eingedampft und der Rückstand im Molekularkolben bei 0,01 mm destilliert. Ein Vorlauf wurde bis 130° Badtemperatur abgetrennt. Bei 135—140° Badtemperatur ging dann der gesuchte Ester als farbloses, dickes Öl über (1,275 g). Das Destillat wurde in absolutem Äther gelöst. Beim Stehen dieser Lösung schied sich eine Spur freies β-Alanin in farblosen Nadeln ab, die abfiltriert wurden. Das eingedampfte Filtrat wurde im Vakuum getrocknet und zeigt eine spez. Drehung von $[\alpha]_D^{20}$ = +36,8° ± 0,5° (c = 1,68 in absolutem Alkohol).

(−)-Pantothensäure-äthylester (V, R = C_2H_5).

Der analog hergestellte Ester wurde ebenfalls als farbloses, in absolutem Äther lösliches Öl erhalten. Die spez. Drehung betrug $[\alpha]_D^{20}$ = −37,3° ± 0,5° (c = 1,565 in absolutem Alkohol).

Chininsalz der (+)-Pantothensäure.

0,5 g (+)-Pantothensäure-äthylester (IV, R = C_2H_5) wurde unter Kühlung mit der berechneten Menge wässeriger Bariumhydroxydlösung versetzt und 48 Stunden bei Zimmertemperatur stehen gelassen. Dann wurde mit Kohlendioxyd neutralisiert, wobei aber keine nennbare Menge von Bariumcarbonat ausfiel. Die Mischung wurde im Vakuum zur Trockne eingedampft, der Rückstand in absolutem Alkohol aufgenommen, von wenig unlöslichen Flocken abfiltriert und mit so viel Aceton versetzt, bis keine weitere Fällung mehr eintrat. Das als weisses Pulver ausgefallene Bariumsalz wurde abgenutscht, mit Aceton und Äther gewaschen und im Vakuum getrocknet. Die Ausbeute war fast quantitativ.

0,5 g des Bariumsalzes wurden in Methanol gelöst und heiss mit der heissen Lösung von Chininsulfat in Methanol genau ausgefällt, wozu etwa 0,68 g Chininsulfat nötig waren. Das Bariumsulfat wurde durch Zentrifugieren entfernt und die klare Lösung im Vakuum eingedampft. Der Rückstand wurde mit wenig Aceton verflüssigt und 2 Tage bei 0° stehen gelassen. Er war hierauf zu einem Krystallkuchen erstarrt, der mit einer Mischung von Aceton und Äther verrieben wurde. Es wurde abgenutscht und mit derselben Mischung gewaschen. Die rohen Krystalle wurden in wenig Wasser bei 0° gelöst, wobei ausser Spuren von Bariumsulfat noch wenig Krystalle unbekannter Zusammensetzung ungelöst blieben. Es wurde über eine Spur Kieselgur filtriert, das klare Filtrat im Vakuum eingedampft, der Rückstand in wenig heissem Aceton gelöst und angerieben. Es trat sofort Krystallisation ein, die durch Stehen bei 0° und vorsichtigen Zusatz von

etwas Äther noch vervollständigt wurde. Zur Analyse wurde das abfiltrierte Produkt nochmals aus wenig heissem Aceton umkrystallisiert. Die farblosen Nadeln schmolzen bei 136—137°. Die spez. Drehung betrug $[\alpha]_D^{20}$ = —95° ± 2° (c = 0,937 in Wasser). Das Salz enthält 1 Mol Krystallwasser, das schwer wegzutreiben ist. Zur Analyse wurde es im Exsikkator bei Zimmertemperatur über Calciumchlorid ohne Vakuum getrocknet.

[illegible],938 mg Subst. gaben 8,909 mg CO_2 und 2,840 mg H_2O
[illegible],928 mg Subst. gaben 0,265 cm³ N_2 (28°, 748 mm)
$C_{29}H_{41}O_7N_3 \cdot H_2O$ (561,66) Ber. C 62,01 H 7,72 N 7,49%
Gef. „ 61,71 „ 7,50 „ 7,52%

Eine weitere Probe wurde bei 80—100° im Hochvakuum bis zur Gewichtskonstanz getrocknet.

[illegible],294 mg Subst. gaben 10,035 mg CO_2, 2,950 mg H_2O und 0,005 mg Rückstand
[illegible],165 mg Subst. gaben 0,272 cm³ N_2 (21,5°, 768 mm)
$C_{29}H_{41}O_7N_3$ (543,64) Ber. C 64,07 H 7,60 N 7,73%
Gef. „ 63,65 „ 7,70 „ 7,85%

Chininsalz der l(—)-Pantothensäure.

Die Herstellung des Bariumsalzes und die Umsetzung desselben mit Chininsulfat geschah genau wie beim Salz der d(+)-Säure. Das rohe Chininsalz krystallisierte aber sofort und liess sich mit Aceton, in dem es sehr schwer löslich ist, gut auswaschen. Es krystallisiert aus Alkohol oder aus wenig Wasser. Zur Analyse wurde zweimal aus absolutem Alkohol umkrystallisiert und mit Aceton gewaschen. Die feinen, farblosen, verfilzten Nädelchen schmolzen bei 183—183,5° und zeigten eine spez. Drehung von $[\alpha]_D^{20}$ = —121° ± 2° (c = 1,312 in Wasser). Auch dieses Salz ist schwer ganz trocken zu erhalten, obschon es kein einheitliches Hydrat darstellt. Zur Analyse wurde 20 Stunden bei 80° im Hochvakuum getrocknet.

[illegible],664 mg Subst. gaben [illegible],029 mg CO_2 und 2,680 mg H_2O
[illegible],226 mg Subst. gaben 0,294 cm³ N_2 (27°, 749 mm)
$C_{29}H_{41}O_7N_3$ (543,64) Ber. C 64,07 H 7,60 N 7,73%
Gef. „ 63,77 „ 7,47 „ 7,80%

Die Mikroanalysen wurden im mikroanalytischen Laboratorium der Firma *F. Hoffmann-La Roche & Co. A.G.*, Basel (Leitung Priv.-Doz. Dr. [illegible]) ausgeführt.

Pharmazeutische Anstalt der Universität Basel.

... Äthanol, Äther, Acetal usw. wurde die katalytische Hydrierung von ... mit Platinoxyd [nach Adams] unter Druck im Autoklaven bei 20—30° ... hydriert und durch das Cyanessigsäure-ester-Verfahren unter den angegebenen ... Bedingungen die CN-Gruppe durch eine Aminogruppe hydriert. Der gebildete ... Alaninester wurde, ohne ihn zu isolieren, verseift und als solcher so ... fort durch Verreibung mit Ammoniak oder Baryt wurde aus ihm reines ... β-Alanin gewonnen. Die Isolierung des Esters ist nicht notwendig, wenn freies ... Alanin dargestellt werden soll.

... platinoxyd als Katalysator wurde bereits von W. H. Carothers [1] zur ... Hydrierung von Nitrilen mit 2 C-Atomen benutzt und mit Erfolg angewandt. ... Besonders gute Ergebnisse wurden durch Zusatz von Essigsäureanhydrid als ... Lösungsmittel erzielt, wobei Acetylderivate entstehen. Allerdings bildeten sich dann die Acetyl-Verbindungen der Amine. Eine Erhöhung der Ausbeute durch Schwefelsäure als Lösungsmittel bei der Hydrierung von Nitrilen machte bereits K. Zindler [2].

Beschreibung der Versuche.

[1] **β-Alanin** [3]. Unter 20 g Cyanessigsäure-ester, einmal destilliert, wurden in 400 ccm Eisessig + 20 ccm konz. Schwefelsäure im Autoklaven in Gegenwart von 3 g PtO_2 unter 30 atü H_2-Anfangsdruck bei 20° ... stunden bis zum Ende der Wasserstoff-Aufnahme geschüttelt. ... waren etwa 3 Mol Wasserstoff aufgenommen worden. Nach dem Abkühlen des Autoklaven wurde der Eisessig im Vak. (12 mm) verdampft. Der Rückstand wurde mit 75 g Eis versetzt, mit Natronlauge gegen ... unter Kühlung mit Kältegemisch vorsichtig unter Rühren versetzt ... und Lösung schwach alkalisch eingestellt (pH 9). Nun wurden ebenfalls ... unter Kühlung 500 g Kaliumcarbonat (entwässert) portionsweise ... zugegeben. Dabei entstand ein steifer Brei, dem durch Behandeln mit Äther ... β-Alaninäthylester recht vollständig entzogen werden konnte. Die ätherische Lösung wurde mit Kaliumcarbonat getrocknet, ... filtriert und ... Nach dem Verdampfen des Äthers im Vak. [3] ... β-Alaninäthylester ... [4].

... β-Alanin. Die Hydrierung von ... wurde wie unter ... angegeben vorgenommen. ... wurden mit ... in 300 ccm Wasser gelöst und mit 200 g feuchtem Bariumhydroxyd versetzt. Nachdem dann 3 Stdn. zum Sieden ... erhitzt und ... mit verd. Schwefelsäure das Barium genau ausgefällt. Die vom Bariumsulfat durch Zentrifugieren befreite Lösung wurde im Vak. fast konzentriert. Das β-Alanin kristallisierte ... mit ... und ... aus ... [5].

... [1] ... [2] ... [3] ... [4] ... [5] ...

Polyoxy-acyl-derivate des β-Alanins

von T. Reichstein und A. Grüssner.

(10. V. 40.)

Die Polyoxy-acyl-derivate des β-Alanins haben in letzter Zeit erheblichen Interesse erlangt, da *Williams* und Mitarbeiter[1]) sowie *Woolley* und Mitarbeiter[2]) zeigten, dass Pantothensäure auch in seine aliphatische Dioxysäure und β-Alanin gespalten lässt. Die Isolierung und Reinigung natürlicher Pantothensäure bereitet ausserordentliche Schwierigkeiten[3]). Die vollständige Reinigung ist bis heute nicht gelungen. Trotzdem konnten *Williams* und Mitarbeiter[4]) durch Anwendung speziell ausgewählter Untersuchungsmethoden zunächst die empirische Bruttoformel, sowie die funktionellen Gruppen festlegen und in jüngster Zeit die Konstitution im Sinne der Strukturformel (I) aufklären[5]).

Viele biologische Fragen, die wegen der schweren Isolierung und Reinigung dieser interessanten Substanz heute noch ungelöst sind, dürften nun bald durch Verwendung synthetischen Materials abgeklärt werden. Die Herstellung von Stoffen vom Typus der Pantothensäure, also von Dioxy-acyl-derivaten des β-Alanins, ist in letzter Zeit bereits in der Literatur erwähnt worden. So schreiben *Woolley* und Mitarbeiter[2]), dass sie die durch Spaltung von natürlicher Pantothensäure erhaltene Dioxysäure wieder mit β-Alanin zu aktiver Pantothensäure vereinigen konnten. *Sabbarow* und *Krane*[6]) geben an, dass sie aus 2,4-Dioxy-valeriansäure mit β-Alanin ein Derivat erhielten, das auf hämolytischen Streptococcen die Wirksamkeit der Pantothensäure zeigte. In beiden Fällen wurde zur Synthese die entsprechende Dioxysäure in ihr acetyliertes Chlorid übergeführt, dieses mit β-Alanin-methylester umgesetzt und das Reaktionsprodukt alkalisch verseift. Diese Methode ist für präparative Zwecke nicht günstig, besonders weil die Herstellung der acetylierten Säurechloride umständlich ist und schlechte Ausbeuten liefert.

[1]) R. J. Williams, H. H. Truesdail, E. E. Snell, J. Am. Soc. 61, 1421 (1939).

[2]) D. W. Woolley, H. B. Vickery, E. E. Snell, J. Am. Soc. 61, 977 (1939).

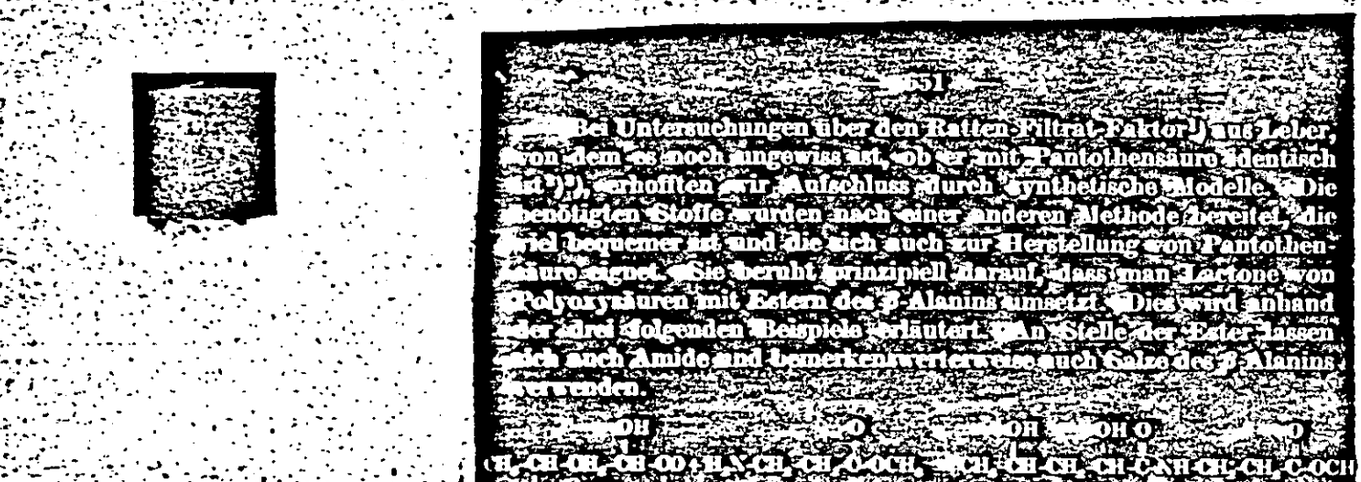
[3]) R. J. Williams, H. H. Truesdail, J. Am. Soc. 61, 1424 (1939); frühere Arbeiten siehe dort.

[4]) R. J. Williams, H. H. Truesdail, J. Am. Soc. 61, 916 (1939).

[5]) Siehe auch R. J. Williams, J. Am. Soc. 61, 1616 (1939).

[6]) J. Sabbarow, H. B. Krane, Am. Soc. 61, 1618 (1939).

Bei Untersuchungen über den Ratten-Filtrat-Faktor[1] aus Leber, von dem es noch ungewiss ist, ob er mit Pantothensäure identisch ist[2], erhofften wir Aufschluss durch synthetische Modelle. Die benötigten Stoffe wurden nach einer anderen Methode bereitet, die viel bequemer ist und die sich auch zur Herstellung von Pantothensäure eignet. Sie beruht prinzipiell darauf, dass man Lactone von Polyoxysäuren mit Estern des β-Alanins umsetzt. Dies wird anhand der drei folgenden Beispiele erläutert. An Stelle der Ester lassen sich auch Amide und bemerkenswerterweise auch Salze des β-Alanins verwenden.



Bereitet man aus den Lactonen (IIa), (IIb) oder (IIc) mit β-Alanin-methylester (IIIa) in Methanol, so ist die Umsetzung nach einer Stunde beendet, und man erhält in ausgezeichneter Ausbeute die Methylester (IVa), (IVb), (IVc). Sie stellen farblose, dickflüssige Öle dar, die sich im Hochvakuum unzersetzt destillieren lassen. Durch vorsichtige, alkalische Verseifung werden daraus die zugehörigen freien Säuren, resp. ihre Salze, gewonnen.

In den oben erwähnten Beispielen wurde bei (IIa) optisch inaktives Material verwendet, sodass auch der Ester (IVa) die dl-Form darstellt. Im Falle von (IIb) handelt es sich um das Gemisch der beiden möglichen Racemformen, demnach stellt auch der Ester (IIIb) ein Gemisch von vier Stereoisomeren dar. Bei (IIc) wurde sowohl inaktives Material, wie die optisch aktiven Formen verwendet. Die letzteren wurden durch Spaltung des Lactons mit Hilfe von Chinin erhalten. Das aus dem schwer löslichen Chininsalz erhaltene linke-

[1] [illegible] Biochem. J. [illegible] 696 (1937); [illegible] Nature [illegible] 111 (1938).
[2] [illegible] Biochem. J. [illegible] 2200 (1938); [illegible] Nature [illegible] 111 (1938).
[illegible] [illegible] 615 (1939).
[illegible] 681 (1939).

drehende Lacton zeigte eine spez. Drehung von: $[\alpha]_D^{15} = -15{,}3° \pm 2°$ (c = 2,8 in Aceton) und war voraussichtlich optisch rein. Der daraus bereitete Ester (IVc) zeigte eine spez. Drehung von: $[\alpha]_D^{15} = +37{,}1°$ (c = 2,047 in Aceton).

Das aus dem leicht löslichen Chininsalz gewonnene Lacton zeigte eine spez. Drehung von $[\alpha]_D^{15} = +11{,}3° \pm 2°$ und war voraussichtlich optisch nicht ganz rein.

Über die Resultate der biologischen Prüfung wird später berichtet. Hier mag nur folgendes bemerkt werden: An Ratten zeigten die beiden Ester (IVa) und IVb) nur höchstens dieselbe geringe Wirksamkeit wie freies β-Alanin[1]). Nach vorläufigen, nicht abgeschlossenen Versuchen wirkt sowohl 2,4-Pantothensäure wie das Lacton (IIc) viel stärker. Für die Prüfung von Konzentraten aus Leberextrakt ist der Rattentest aber unangenehm, da er lange dauert und wenig spezifisch ist. Es wurde daher für die Untersuchungen über den Leber-Filtrat-Faktor im letzten Jahre von uns ein Mikro-Organismus, und zwar ein besonderes Essigbakterium, als Testobjekt verwendet, welches auf einem geeigneten Nährboden erst nach Zugabe von Hefeextrakt oder Leberextrakt wächst und das auf β-Alanin gar nicht anspricht. An diesen Bakterien erwiesen sich die Ester (IVa) und (IVb), sowie die daraus gewonnenen Säuren als völlig unwirksam. Gut wirksam waren das Lacton (IIc), der Ester (IVc) und die daraus gewonnene Säure (I) (als Natriumsalz), besonders wenn etwas Nicotinsäure-amid als Ergänzung gegeben wurde. Dies erklärt die Tatsache, dass die Wirksamkeit unserer Konzentrate aus Leberextrakt gegenüber diesem Testobjekt durch energische Verseifung mit Alkali nicht zerstört wurde, obwohl die Löslichkeitseigenschaften durch diese Behandlung stark geändert werden. Der wirksame Stoff liess sich nämlich aus intakten Leberextrakten mit Phenol (sowohl aus neutraler wie aus saurer Lösung) ausschütteln. Mit Butylalkohol gelang es jedoch, aus solchen Extrakten auch bei stark saurer Reaktion nur einen sehr geringen Teil der Aktivität auszuschütteln. Wurden die ursprünglichen oder besser die durch Phenolextraktion vorgereinigten Extrakte aber durch 2-stündiges Erhitzen mit 2-n. Natronlauge auf 100° verseift, so liess sich nach dem Ansäuern die ganze Aktivität mit Butyl- oder tert.-Amylalkohol ausschütteln.

Wir danken der Firma F. Hoffmann-La Roche & Co. A.-G. für die Unterstützung dieser Arbeit.

Experimenteller Teil.

2,4-Dioxy-valeriansäure-lacton (IIa).

Es wurde prinzipiell nach dem Verfahren von *Fittig*[2]) gearbeitet, dieses aber in Anlehnung an die von *Hudson*[3]) für analoge Fälle ausgearbeitete Methodik wie folgt abgeändert:

10 g frisch im Vakuum destilliertes Aldol wurden bei 0° in die Lösung von 7 g Natriumcyanid und 8 g Calciumchlorid (auf wasserfreies Material berechnet) in 100 cm³ Wasser eingetragen und zunächst 6 Stunden bei 0°, dann noch 16 Stunden bei Zimmertemperatur stehen gelassen. Das Reduktionsvermögen war dann verschwunden. Hierauf wurde die Lösung von 10 g Natriumhydroxyd in wenig Wasser zugegeben und die Mischung im Ölbad mehrere Stunden gekocht, bis die Ammoniakentwicklung beendigt war. Dann wurde abgekühlt, mit konz. Salzsäure bis zur rein blauen Reaktion auf

[1]) *M. Hoffer, T. Reichstein*, Nature 144, 72 (1939).

[2]) *R. Fittig, W. Lepère*, A. 334, 85 (1904).

[3]) *C. S. Hudson, O. Hartley, C. B. Purves*, Am. Soc. 56, 1248 (1934).

Kongo versetzt und zur Entfernung kleiner Mengen von Verunreinigungen zunächst zweimal mit Äther ausgeschüttelt. Die verbleibende wäßrige Lösung wurde hierauf so oft mit tertiärem Amylalkohol ausgeschüttelt, bis eine Probe des letzten Auszuges beim Eindampfen keinen Rückstand mehr hinterließ. Die Auszüge wurden mit Natriumsulfat getrocknet, im Vakuum eingedampft und der Rückstand im Hochvakuum destilliert. Nach zweimaliger Destillation wurden 3,6 g analysenreines Lacton vom Sdp. 89° bei 0,2 mm erhalten.

[illegible] (116,11) Ber. C 61,81 H 6,95%
Gef. „ 61,15 „ 7,13%

[illegible] mld. 1 g Lacton wurde in 3 ccm Methanol gelöst, mit trockenem Ammoniakgas gesättigt und gut verschlossen 48 Stunden stehen gelassen. Hierauf wurde eingedampft und der Rückstand im Exsikkator getrocknet. Es trat bald Kristallisation ein. Das rohe Produkt schmolz bei 70—100° und nach zweimaligem Umkristallisieren aus Methanol-Äther immer noch sehr unscharf bei 80—100°. Erst nach mehrmaligem Umkristallisieren aus Methanol-Äther, dann aus Essigester, wurde ein ziemlich scharfer Smp. von 103—105° korr. erhalten. Das Lacton dürfte daher ein Gemisch der beiden stereoisomeren 2,4-Formen sein. *Wieck* und *Wagner*) geben für ein aus Holzteer isoliertes 2,4-Dioxy-valeriansäure-amid den Smp. 99—100° an, für ein nach *Pittig* bereitetes Produkt, das mit dem vorigen eine starke Schmelzpunktserniedrigung gibt, den Smp. 105—106°.

[illegible]-Dioxy-valeriansäure-lacton aus Allyl-essigsäure.

10 g Allyl-essigsäure wurden in 150 ccm Wasser gelöst, mit 75 g Silberchlorat und, nachdem dieses in Lösung gegangen war, mit 50 mg Osmiumtetroxyd versetzt. Die Mischung blieb kurze Zeit klar, dann begann sich reichlich Silberchlorid abzuscheiden, und nach 16 Stunden war leichte Bräunung eingetreten. Es wurde filtriert, das Filtrat im Vakuum auf 50 ccm eingeengt, mit Salzsäure bis zur stark Kongosauren Reaktion versetzt und zweimal mit Essigester ausgeschüttelt. Der Essigester hinterließ beim Eindampfen 0,5 g Rückstand, der langsam kristallisierte. Die saure wäßrige Lösung wurde hierauf sechsmal mit je 100 ccm tertiärem Amylalkohol ausgeschüttelt, die Auszüge mit Natriumsulfat getrocknet, im Vakuum eingedampft und der Rückstand im Hochvakuum gut getrocknet. Erhalten wurden 9,8 g farbloser Syrup, der wie folgt über das Cadmiumsalz gereinigt wurde. Er wurde 2 Stunden mit überschüssiger, wäßriger Barytlösung erwärmt und der Überschuß hierauf mit Kohlendioxyd ausgefällt. Es wurde aufgekocht, heiß filtriert und das heiße Filtrat genau mit der nötigen Menge heißer Cadmiumsulfatlösung versetzt, bis eine ausgetrunkene Probe weder Barium- noch

[illegible] Ozean. Chem. 7, 87 (1867); C. [illegible]

Sulfat-Ionen enthielt. Dann wurde über wenig Kohle abgenutscht und das klare Filtrat im Vakuum vollständig eingedampft. Der Rückstand wurde in heissem Methanol gelöst, durch Filtration von wenig unlöslichem Material befreit und bis zur Krystallisation stehen gelassen. Beim Impfen trat diese sofort ein. Die Krystalle wurden abgenutscht und mit Methanol und Äther gewaschen. Die Ausbeute betrug 3,5 g. Zur Analyse wurde eine Probe aus Wasser-Methanol umkrystallisiert und im Hochvakuum bei 100° getrocknet. Das Salz schmilzt bei raschem Erhitzen bei etwa 193° unter Zersetzung und wird hierauf wieder fest. Bei langsamem Erhitzen tritt keine Schmelze, sondern nur allmähliche Zersetzung ein.

[illegible] H_2O (378.68) Ber. C 31.72 H 5.79 Cd 29.69%
Gef. „ 31.69 „ 5.14 „ 28.15%

Das Cadmiumsalz wurde in heissem Wasser gelöst und mit Schwefelwasserstoff zerlegt. Das Cadmiumsulfid wurde hierauf über wenig Kohle abgenutscht, das Filtrat im Vakuum eingedampft und der Rückstand zweimal im Hochvakuum destilliert. Es wurden 3,2 g farbloses Öl erhalten vom Sdp. 100° bei 0,1 mm. Grössere Mengen wurden einfacher nach der Vorschrift von *Leuchs*[1]) hergestellt. Das so bereitete Lacton gab dasselbe Cadmiumsalz.

[illegible]-1,2,5-Dioxy-valeriansäure-lacton (IIb).

Dieses Lacton wurde in geringer Abänderung seiner Vorschrift, die uns von der Firma *F. Hoffmann-La Roche & Co.* zur Verfügung gestellt wurde, wie folgt bereitet:

100 g [illegible]-Chlorpropyl)-brom-malonsäure-diäthylester[2]) wurden in 100 ccm 96-proz. Alkohol gelöst und mit 800 g wässriger 33,3-proz. Natronlauge versetzt. Beim Umschütteln ging der Ester zunächst mit gelblicher Farbe in Lösung, dann erstarrte alles unter leichter Erwärmung zu einem dicken Krystallbrei. Es wurden 200 ccm Wasser zugegeben und die Mischung 12 Stunden unter Rückfluss gekocht. Hierauf wurde nochmals mit 100 ccm Wasser versetzt und der Alkohol vollständig abdestilliert. Nach dem Erkalten wurde mit konz. Salzsäure bis zur stark kongosauren Reaktion versetzt und unter Rückfluss so lange gekocht, bis die Gasentwicklung beendigt war. Dann wurde im Vakuum zur Trockne gedampft, der Rückstand sechsmal mit warmem Methylalkohol ausgezogen und diese Auszüge eingedampft. Der Rückstand wurde wieder sechsmal mit warmem Essigester ausgezogen, die Lösung filtriert, im Vakuum eingedampft und der Rückstand im Hochvakuum destilliert. Nach zweimaliger Fraktionierung wurden 23 g farbloses Öl vom Sdp. 70° bei 0,1 mm oder 123—125° bei 10 mm Druck erhalten.

[illegible] Chem. Ber. [illegible], 1228 (1909).

[illegible] Chem. Ber. [illegible], 121 (1913).

Das Amid kristallisierte gut, war aber äusserst hygroskopisch. Zur Charakterisierung besser geeignet ist das

Phenylhydrazid. 0,3 g 4,2,5-Dioxy-valeriansäure-lacton wurden mit 0,44 g Phenylhydrazin in 5 ccm absolutem Alkohol 1 Stunde unter Rückfluss gekocht. Die Lösung färbte sich leicht orange. Hierauf wurde im Vakuum eingedampft und der Rückstand mit Äther bis zum Auftreten der ersten Trübung versetzt. Sehr bald trat Kristallisation ein. Die Kristalle wurden mit Äther gewaschen und aus Alkohol-Äther umkristallisiert. Die farblosen Nadeln schmolzen bei 106—107° korr. Zur Analyse wurde bei 0,0005 mm und 70° Blocktemperatur sublimiert.

$C_{11}H_{14}O_3N_2$ (222,25) Ber. C 59,91 H 7,19 N 12,49%
Gef. „ 59,71 „ 7,25 „ 12,77%

4,2-Oxy-2,2-dimethyl-butyrolacton (IIc).

Dieses Lacton wurde von *Glaser*[1]) aus 2-Oxy-2,2-dimethyl-propion-aldehyd[2]) mittelst der Cyanhydrin-Reaktion bereitet. Wir benützten hierzu die bei der Herstellung von (IIa) beschriebene Modifikation. Das so bereitete Lacton destillierte im Vakuum von 11 mm bei 120°. Es erstarrte sofort und schmolz roh bei 75—78°. *Glaser* gibt einen Smp. von 35° an. Da das Produkt aber sehr hygroskopisch ist, sollte auf diesen Unterschied kein zu grosser Wert gelegt werden. Das Phenylhydrazid kristallisierte bisher nicht. Ebensowenig gelang es, mit Diphenylhydrazin, p-Nitro-phenylhydrazin und Hydrazin kristallisierte Derivate zu bereiten. Leicht kristallisiert hat bisher nur das

Amid. Dieses wurde wie das von (IIa) hergestellt und aus Methanol-Äther umkristallisiert. Es schmolz bei 123—124° korr. Zur Analyse wurde im Hochvakuum bei 125° Blocktemperatur sublimiert.

$C_6H_{11}O_3N$ (145,17) Ber. C 48,96 H 8,90 N 9,52%
Gef. „ 48,82 „ 8,40 „ 9,50%

Spaltung in optische Antipoden. 3 g Lacton wurden in 5 ccm Wasser gelöst und mit der Lösung von 3,5 g Chinin in 7 ccm Alkohol 6 Stunden unter Rückfluss gekocht. Hierauf wurde der Alkohol im Vakuum abdestilliert, die grüne wässrige Lösung zur Entfernung von Chinin zweimal mit Äther ausgeschüttelt und im Vakuum auf ein kleines Volumen eingeengt. Es kristallisierten 1,15 g Salz vom Smp. 185—186° in langen Prismen. Dieses Salz wurde aus Wasser-Methanol umkristallisiert und gab 1,2 g Kristalle vom Smp. 186—187° (Salz A). Die wässrigen Mutterlaugen wurden im Vakuum ganz eingedampft und der Rückstand zweimal aus Methanol-Äther (1:6) umkristallisiert. Es wurden 1,3 g wollige Nadeln vom Smp. 177—178° erhalten (Chininsalz B). Aus den letzten Mutterlaugen, die noch freies Lacton enthielten, konnten durch nochmaliges Kochen mit Chinin weitere Mengen der beiden Salze erhalten werden.

[1]) *Glaser*, A. **275**, 7 (1893). [2]) *Favorski*, A. **214**, 118 (1900).

Linksdrehendes Lacton. 2 g Chininsalz (A) vom Smp. 186—187° (korr.) wurden in Methanol-Wasser gelöst und mit der wässrigen Lösung von 1,2 g Bariumhydroxyd versetzt. Das ausgefällte Chinin wurde durch Ausschütteln mit Chloroform und Äther entfernt. Aus der wässrigen Lösung wurde das Bariumion mit Schwefelsäure ganz genau ausgefällt. Nach Filtration über eine Spur Kohle wurde die klare wässrige Lösung im Vakuum eingedampft und der Rückstand im Molekularkolben bei 0,01 mm Druck und 100° Badtemperatur sublimiert. Erhalten wurden 80 mg Lacton, das sofort auskristallisierte, aber sehr hygroskopisch war. Es schmolz bei 80—85°. Aus Äther-Pentan liess es sich umkristallisieren. Die spez. Drehung einer umkristallisierten Probe betrug: $[\alpha]_D^{20} = -15,3° \pm 2°$ (c = 2,80 in Aceton):

[illegible] mg ± 0,3 mg Substanz in 0,0994 cm³; l = 1 dm; $\alpha_D^{20} = -0,43° \pm 0,02°$.

Amid des linksdrehenden Lactons. 40 mg linksdrehendes Lacton wurden wie bei der inaktiven Verbindung ins Amid überführt. Dieses wurde aus Methanol-Äther umkristallisiert und schmolz bei 124—124,5°. Die Mischprobe mit dem gleichschmelzenden inaktiven Amid schmolz bei 118—120°.

Rechtsdrehendes Lacton. 2 g Chininsalz (B) vom Smp. 176—177° wurden ganz wie das Salz (A) zerlegt. Das erhaltene Lacton wurde zweimal im Hochvakuum sublimiert und schmolz bei 78—80° nach vorhergehendem Sintern bei 70°. Die spez. Drehung betrug: $[\alpha]_D^{20} = +13° \pm 2°$ (c = 1,68 in Aceton).

[illegible] mg ± 0,3 mg Substanz in 0,0994 cm³; l = 1 dm; $\alpha_D^{20} = +0,19° \pm 0,02°$.

Amid des rechtsdrehenden Lactons. Dieses wurde wie die anderen Amide bereitet. Nach Sublimation und Umkristallisieren aus Methanol-Aceton-Äther schmolz es bei 124—124,5°. Es zeigte keine merkbare optische Drehung, sowohl bei Natriumlicht wie bei grünem Quecksilberlicht wurde $[\alpha]_D = 0° \pm 2°$ (c = 1,68 in Methanol) gefunden.

2,4-Dioxy-valeroyl-2-alanin-methylester (Ve). 1 g 2,4-Dioxy-valeriansäure-lacton (IIe) wurden in 2 ccm Methanol gelöst und in das siedende Gemisch der Lösung von 0,8 g frisch im Vakuum destilliertem 2-Alanin-methylester (Sdp. 60 mm, [illegible]) in 2 ccm Methanol langsam eingetropft. Anschliessend wurde noch 1 Stunde unter Rückfluss gekocht. Dann wurde im Vakuum eingedampft und der Rückstand im Molekularkolben bei 0,001 mm destilliert. Bei einer Badtemperatur bis 100° wurde zunächst ein

[illegible] Soc. [illegible], 478 (1919); [illegible] (1893); [illegible] (1906).

kleiner Vorlauf abgetrennt. Die Hauptmenge ging bei 135—140° Badtemperatur über. Es wurden 1,1 g farbloses, dickes Öl erhalten.

$C_{11}H_{21}O_4N$ (219.28) Ber. N 6.39 Gef. N 6.58%.

Verseifung. Zur biologischen Prüfung wurde eine Probe wie folgt verseift. 50 mg Ester wurden mit der Lösung von 20 mg Natriumhydroxyd in 2,3 cm³ Wasser 6 Stunden bei Zimmertemperatur stehen gelassen. Dann wurde mit Salzsäure genau neutralisiert und direkt zur Prüfung verwendet.

d,l-2,3-Dioxy-valeroyl-β-alanin-methylester (IVb).

Der Ester wurde, genau wie beim 2,4-Dioxy-derivat beschrieben, gewonnen. Zur Analyse wurde im Molekularkolben bei 0,001 mm und 135° Badtemperatur destilliert. Der Ester stellt ein farbloses, dickes Öl dar.

Analog wurde der entsprechende Äthylester bereitet.

$C_{10}H_{19}O_4N$ (233.26) Ber. N 6.00 Gef. N 6.09%.

Für biologische Versuche wurde wiederum eine Probe alkalisch verseift.

d,l-2,4-Dioxy-β,β-dimethyl-butyroyl-β-alanin-methylester (IVc).

(d,l-Pantothensäure-methylester.)

1,2 g d,l-4-Oxy-β,β-dimethyl-butyrolacton und 1,25 g β-Alanin-methylester wurden in 8 cm³ Methanol 1 Stunde unter Rückfluss gekocht. Dann wurde im Vakuum eingeengt und der Rückstand im Molekularkolben im Hochvakuum destilliert. Unter 0,001 mm Druck wurde bis 100° Badtemperatur ein kleiner Vorlauf abgetrennt. Die verbleibende Substanz ging bei einer Badtemperatur bis 130° vollständig als farbloses, dickes Öl über.

$C_{11}H_{21}O_5N$ (247.28) Ber. C 51.49 H 8.22 N 5.66%

Gef. „ 51.15 „ 8.42 „ 5.17%.

Eine Probe des Esters wurde für biologische Versuche, wie bei dem Homologen beschrieben, alkalisch verseift.

Optisch aktive Formen. Die optisch aktiven 4-Oxy-β,β-dimethyl-butyrolactone wurden genau so mit β-Alanin-methylester umgesetzt. Der aus dem linksdrehenden Lacton $[\alpha]_D^{20} = -15,3°$ erhaltene Ester (IVc) zeigte eine spez. Drehung von $[\alpha]_D^{20} = +37,1° \pm 1°$ (c = 2,017 in Aceton). Ob teilweise Racemisierung eingetreten ist, soll später geprüft werden.

Die Mikroanalysen wurden im Laboratorium der Firma F. Hoffmann-La Roche & Cie. AG., Basel, ausgeführt.

Pharmazeutische Anstalt der Universität Basel.

CONSOLIDATED VULTEE AIRCRAFT CORPORATION

STINSON DIVISION
WAYNE, MICHIGAN

July 15, 1946

Mr. Brothman, Chief Engineer
A. BROTHMAN AND ASSOCIATES
114 East 32 Street
New York 16, New York

Dear Mr. Brothman:

Your inquiry about the four-place Stinson "Voyager 150" was welcomed here as further proof that the people who fly want an airplane with speed, utility, and load carrying capacity. Because Stinson engineers kept these requirements before them, the "Voyager 150" meets all of your expectations for a postwar plane.

The "Voyager 150" takes off in 550 feet, climbs at 770 feet per minute, and cruises at 125 miles an hour. The range is more than 500 miles, and the useful load is 944 pounds. Powered by a six cylinder horizontally opposed Franklin engine, the "Voyager" can take off from short fields carrying capacity loads. In a word, it's a working airplane that will provide you with fast, direct and economical transportation.

The price of the "Voyager 150" is $5495 at the factory with the two-way radio, two landing lights, the antenna and fixed loop installed. Since there is a Stinson representative in the territory where you reside, we are forwarding your inquiry to him.

Thanks for your interest in Stinson and the "Voyager 150".

Sincerely yours,

STINSON, Division of
Consolidated Vultee Aircraft Corp.

Larry Cooper

Larry Cooper
General Sales Manager

LC:dd
Encl:

#5

Received June 6, 1970

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Relationship to Author: Friend

Title: #5 Mumbo Jumbo Number and

Description:

File No. 65-4807-1-B-14

Photocopies

Pyridoxal (P.)

UNITED STATES PATENT OFFICE

2,248,078

PROCESS OF PREPARING VITAMIN B_6

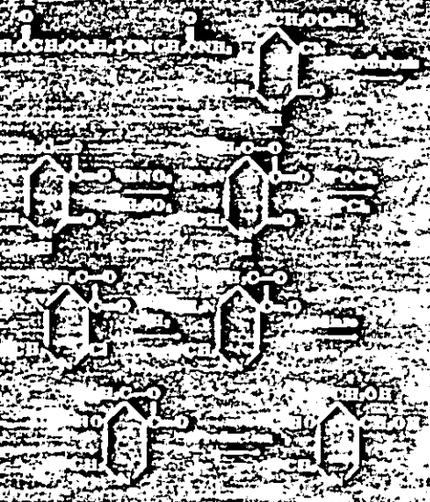
Stanton A. Harris, Haworthed, N. J., assignor to Merck & Co., Inc., Rahway, N. J., a corporation of New Jersey

No Drawing. Application December 17, 1938, Serial No. 247,948

11 Claims. (Cl. 260—295)

This invention relates to a process of preparing vitamin B_6 and related compounds, and to new intermediate products made and employed in such process.

We have discovered that these compounds may be synthesized by reacting ethoxyacetylacetone and cyanoacetamide to form 3-cyano-4-ethoxymethyl-6-methylpyridone-2, hydrolyzing the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-6-methylpyridone-2, treating the latter compound with nitric acid to form the lactone of 3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridone-2, chlorinating the latter compound to form the lactone of 3-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine, reducing the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, the latter alternatively by reducing the lactone of 3-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine to the lactone of 3-chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, and reducing the latter compound to the lactone of 3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, diazotizing the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-5-hydroxy-6-methylpyridine, and reducing the latter compound to form vitamin B_6. These steps may be represented by the following:



The following example illustrates one method

It is to be understood that the example is given by way of illustration and not of limitation.

Sixty-five and three tenths gms. of cyanoacetamide are dissolved in 600 cc. of hot 95% alcohol and 93.1 gms. of ethoxyacetylacetone are added. Twenty-five cc. of piperidine are then added with shaking, whereupon the mixture becomes warm. The solution is cooled and allowed to stand overnight, again cooled, and filtered. The crystals are washed with 95% alcohol and a yield of 92 gms. or 31% of white crystals is obtained, having a melting point of 200–202° C. Upon recrystallization from boiling 95% alcohol, crystals of 3-cyano-4-ethoxymethyl-6-methylpyridone-2 are obtained, which have a melting point of 202.5° C.

Fifteen gms. of 3-cyano-4-ethoxymethyl-6-methylpyridone-2 are mixed with 125 cc. of concentrated hydrochloric acid and heated at 120–125° C. for four hours, the reaction mixture is poured into 400 cc. of a mixture of water and ice, whereupon crystals of the lactone of 3-carboxy-4-hydroxymethyl-6-methylpyridone-2 appear. The mass is filtered and washed with water, the dried product weighing 11.1 gms. or about 87% yield. Upon recrystallization from water the crystals have a melting point of 230° C. (uncorrected).

Alternatively, the lactone of 3-carboxy-4-hydroxymethyl-6-methylpyridone-2 may be obtained by reducing 93 gms. of 3-cyano-4-ethoxymethyl-6-methylpyridone-2 for three hours with 1120 cc. of 50% sulfuric acid, the temperature of the liquid being 120° C. The reaction mixture is poured into 5 liters of water and placed in an ice room overnight. The next day, the crystals are filtered off, washed well with water, alcohol, and ether, and dried at 50° C. The yield is 70.5 gms. or 82% of theory.

Twenty-eight gms. of the lactone of 3-carboxy-4-hydroxymethyl-6-methylpyridone-2 are dissolved in 42 cc. of concentrated sulfuric acid. The solution is cooled and added to an ice cold mixture of 124 cc. of concentrated nitric acid and 53 cc. of fuming nitric acid (sp. gr. 1.5). The mixture forms exothermically, reaching a temperature of 50–55° C. After this temperature has been reached the mixture is cooled to 45° C. and poured onto crushed ice to the final volume of about 1 liter. A yellow solid forms immediately, which is filtered off and dried at 65° C. The yield of the lactone of 3-carboxy-4-hydrox-

...ymethyl-5-nitro-6-methylpyridone-2 is 29.8 gms. ...63.5%. On recrystallization from water, it ...melts at 278–280° C. with decomposition.

...fifteen and three tenths gms. of the lactone ...of 2-carboxy-4-hydroxymethyl-5-nitro-6-methyl-...pyridone-2, 80 cc. of phosphorus oxychloride, ...and ten grams of phosphorus pentachloride ...(75%) are mixed and refluxed until solution ...occurs, which requires about ¾ of an hour. The ...phosphorus oxychloride is distilled off under ...vacuo, whereupon a solid separates. The solid ...is dissolved in benzene, filtered and precipitated ...by the addition of petroleum ether. The total ...yield of the lactone of 2-chloro-3-carboxy-4-...hydroxymethyl-5-nitro-6-methylpyridine is 12.8 ...gms. or 77% of theory. It may be recrystallized ...from benzene and ethyl acetate, and has a melt-...ing point of 176–178° C.

...Two and twenty-eight hundredths gms. of the ...lactone of 2-chloro-3-carboxy-4-hydroxymethyl-...5-nitro-6-methylpyridine are dissolved in 150 cc. ...of a mixture of ethyl acetate and 95% of ethyl ...alcohol, 10 gms. of 5% palladium on barium car-...bonate and 0.3 gm. of platinum oxide are added ...as a catalyst, and the mixture is hydrogenated ...under about two atmospheres pressure. The re-...duction proceeds smoothly and takes up the full ...four mols of hydrogen in about one hour. The ...mixture is filtered and the solvent removed by ...evaporation. The residue is extracted with a ...mixture of water and chloroform. The chloro-...form layer is separated, and the chloroform ...evaporated. The residue is recrystallized from ...ethyl acetate, and is the lactone of 2-carboxy-4-...hydroxymethyl-5-amino-6-methylpyridine; melt-...ing point 225–230° C. The picrate of this com-...pound is made by mixing alcohol solutions of ...the same and picric acid, it is filtered and re-...crystallized from water or alcohol. The picric ...salt has a melting point of 230° C. with decomposi-...tion. Alternatively, 5.53 gms. of the lactone of ...2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-...methylpyridine is dissolved in 150 cc. of glacial ace-...tic acid, 0.3 gm. platinum oxide added and the mix-...ture shaken with hydrogen at three atmospheres ...pressure until three molecular equivalents are ...absorbed. The reduction is stopped, the mixture ...cooled, filtered and recrystallized from glacial ...acetic acid. The total yield of the lactone of ...2-chloro-3-carboxy-4-hydroxymethyl-5-amino-...6-methylpyridine is 3.31 gms. or 68% of theory. ...It may be recrystallized directly from glacial ...acetic acid or from strong hydrochloric acid ...by dilution and has a melting point of 225–230° C. ...with decomposition.

...Five and eighty-five hundredths gms. of the ...lactone of 2-chloro-3-carboxy-4-hydroxymethyl-...5-amino-6-methylpyridine is suspended in 250 cc. ...of absolute alcohol with 10 gms. palladium on ...barium carbonate as a catalyst and shaken with ...hydrogen at 3–4 atmospheres pressure and 90° C. ...until the theoretical quantity is absorbed. The ...solution is filtered from the catalyst and cooled ...whereupon crystals are deposited. Additional ...crystals are obtained by evaporation of the mother ...liquor. The total yield of the lactone of 2-carboxy-...4-hydroxymethyl-5-amino-6-methylpyridine is ...3.9 gms. or 77.5% of theory. The melting point ...is 230–232° C. and it may be recrystallized from ...ethyl acetate.

...The lactone of 2-carboxy-4-hydroxymethyl-5-...amino-6-methylpyridine is dissolved in 20% hy-...drochloric acid and reduced with hydrogen in ...the presence of Raney nickel catalyst at about ...90° C. and three atmospheres pressure. The solu-...tion is filtered from the catalyst, evaporated to ...dryness in vacuo, and the residue is recrystallized ...from alcohol and acetone. The yield of the hydro-...chloride, the water is removed by evaporation, ...and the lactone of 2-carboxy-4-hydroxymethyl-...5-hydroxy-6-methylpyridine is obtained by ex-...traction with alcohol. M. P. 272–3° C. The latter ...compound is dissolved in anhydrous acetic acid ...and sodium amalgam is added until reaction is ...complete. The acetic solution is diluted with ...concentrated hydrochloric acid and refluxed for ...three hours. The solution is then concentrated ...in vacuo and the hydrochloride of vitamin B₆ ...is extracted with alcohol and crystallized by the ...addition of acetone. If desired, the vitamin B₆ ...free base can be obtained from the hydrochloride, ...and has the formula 3,4-di(hydroxymethyl)-5-...hydroxy-6-methylpyridine.

...Alternatively, the lactone of 2-carboxy-4-hy-...droxymethyl-5-hydroxy-6-methylpyridine is dis-...solved in 20% hydrochloric acid and warmed on ...a boiling water bath. Granulated tin is added ...and the mixture heated for one hour. The solu-...tion is evaporated to dryness and the residue ...dissolved in water and treated with hydrogen ...sulphide to remove the tin. The filtrate is again ...evaporated to dryness and the vitamin B₆ hy-...drochloride is recrystallized from alcohol and ...acetone.

...Alternatively, the lactone of 2-carboxy-4-hy-...droxymethyl-5-hydroxy-6-methylpyridine is dis-...solved in water and reduced with hydrogen in ...a high pressure bomb at 175° C. with copper ...chromite as the catalyst. After cooling to room ...temperature the solution is filtered from the ...catalyst and evaporated to dryness to obtain ...vitamin B₆.

...Modifications may be made in carrying out ...this invention without departing from the spirit ...and scope thereof.

...I claim:

...1. In the process of preparing vitamin B₆, the ...steps which comprise reacting ethoxyacetylace-...tone and cyanoacetamide to form 3-cyano-4-...ethoxymethyl-6-methyl-pyridone-2, and convert-...ing the latter by a series of reactions into vita-...min B₆.

...2. In the process of preparing vitamin B₆, the ...steps which comprise hydrolyzing 3-cyano-4-...ethoxymethyl-6-methylpyridone-2 to form the ...lactone of 2-carboxy-4-hydroxymethyl-6-meth-...ylpyridone-2, and converting the latter by a se-...ries of reactions into vitamin B₆.

...3. In the process of preparing vitamin B₆, the ...steps which comprise treating the lactone of ...2-carboxy-4-hydroxymethyl-6-methylpyridone-2 ...with nitric acid to form the lactone of 2-carboxy-...4-hydroxymethyl-5-nitro-6-methylpyridone-2, ...and converting the latter by a series of reactions ...into vitamin B₆.

...4. In the process of preparing vitamin B₆, the ...steps which comprise chlorinating the lactone ...of 2-carboxy-4-hydroxymethyl-5-nitro-6-meth-...ylpyridone-2 to form the lactone of 2-chloro-3-...carboxy-4-hydroxymethyl-5-nitro-6-methyl-...pyridone, and converting the latter by a series of ...reactions into vitamin B₆.

...5. In the process of preparing vitamin B₆, the ...steps which comprise reducing the lactone of 2-...chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-...methylpyridine to form the lactone of 2-chloro-...3-carboxy-4-hydroxymethyl-5-amino-6-meth-...ylpyridone, and converting the latter by a series ...of reactions into vitamin B₆.

...6. In the process of preparing vitamin B₆, the ...steps which comprise reducing the lactone of ...2-chloro-3-carboxy-4-hydroxymethyl-5-amino-...6-methylpyridine to form the lactone of 2-car-

methylpyridine-2- chlorinating the latter compound to form the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6 - methylpyridine, reducing the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine, diazotizing the latter compound to form the lactone of 3-carboxy-4-hydroxymethyl-5-hydroxy-6-methylpyridine, and reducing the latter compound to form vitamin B6.

11. The lactone of 2-chloro-3-carboxy-4-hydroxymethyl-5-nitro-6-methylpyridine.

12. The lactone of 3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine.

13. The lactone of 3-carboxy-4-hydroxymethyl-5-hydroxy-6-methylpyridine.

14. Compounds of the general formula:

wherein R1 is a member selected from the group consisting of nitro, amino, and hydroxy, and R2 is a member selected from the group consisting of chlorine and hydrogen.

STANTON A. HARRIS.

Certificate of Correction

Patent No. 2,348,078. July 2, 1941.

STANTON A. HARRIS

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows: Page 3, second column, lines 17 to 22, claim 10, for the formula

and that the said Letters Patent should be read with this correction therein that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 27th day of April, A. D. 1943.

(SEAL)

HENRY VAN ARSDALE,
Acting Commissioner of Patents.

Patented July 22, 1941 2,250,396

UNITED STATES PATENT OFFICE

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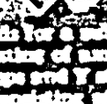

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tion of gas. After ½ hour's standing the excess thionylchloride is distilled off under reduced pressure. The solid residue is rubbed on with a small quantity of ether and filtered with suction. The acidchloride-hydrochloride thus obtained is gradually introduced into 2 liters of 25% aqueous ammonia while stirring. Thereby the acid amide precipitates at once and is filtered off with suction.

100 parts of the 2-methoxy-quinaldine-4-carboxylic acid amide thus obtained are covered by pouring with 500 parts of phosphorus oxychloride and boiled for 2-3 hours while cooling under reflux. Thereby gradually a clear brown solution is obtained. The excess phosphorus oxychloride is evaporated under reduced pressure and the oily residue is poured on to ice. It is now made alkaline to litmus by the addition of ammonia and the nitrile precipitating thereby, dissolved in methylenechloride. The methylenechloride solution is dried with potassium carbonate and the methylenechloride is evaporated from the dry solution. The remaining solid residue is distilled under reduced pressure. The 2-methoxy-quinaldine-4-carboxylic acid nitrile thus obtained distills under 3 mms. pressure at 150° C. as an oil which solidifies to crystals melting at 88° C.

100 parts of this product are shaken with 10 parts of animal charcoal, 10 parts of palladious chloride solution, 500 parts of concentrated hydrochloric acid and 1500 parts of water with hydrogen at room temperature until after the taking up of 2 mols of hydrogen no further hydrogen is taken up any more. The solution is now freed from the animal charcoal by filtration with suction, it is made strongly alkaline with sodium hydroxide solution and the oil precipitated is extracted with methylenechloride. The residue remaining after drying of the methylenechloride solution and the evaporation of the solvent is distilled under reduced pressure. The 2-methoxy-4-aminomethyl-quinaldine thus obtained distills as a colorless liquid under 3 mm. pressure at 154° C.

100 parts of 2-methoxy-4-aminomethyl-quinaldine are dissolved in 500 parts of 4-normal hydrochloric acid and gradually treated while stirring with a solution of 35 parts of sodium nitrite in 150 parts of water at 0° C. The reaction takes place at once with the evolution of nitrogen. After cooling the mixture is made alkaline with ammonia, thereby the 2-methoxy-4-hydroxymethyl-quinaldine precipitates at once in white crystals, melting at 138° C. which are separated by sucking off.

10 parts of 2-methoxy-4-hydroxymethyl-quinaldine are dissolved in 100 parts of hydrochloric acid (specific gravity = 1.7) and heated for half an hour to 80° C. The hydrochloric acid is evaporated under reduced pressure, the solid residue is covered by pouring with a solution of 20 parts of sodium in 150 parts of methanol and the mixture is then heated for half an hour on the water-bath. After the addition of 150 parts of water the methanol is evaporated under reduced pressure and the remaining solution is shaken out with methylenechloride. The methylenechloride solution is dried by means of sodium sulphate, the methylenechloride is evaporated and the 2-methoxy-4-methoxymethyl-quinaldine thus obtained is distilled under reduced pressure. It boils at 160° C. under 3 mms. pressure and solidifies to crystals melting at 50° C.

and part of 2-methoxy-4-methoxymethyl-quinaldine is introduced while cooling with ice into 10 parts of nitric acid (specific gravity = 1.5). The solution obtained is at once poured on to ice and the mixture is made alkaline with ammonia. Thereupon the nitration product precipitates at first as a yellow oil which after some storing solidifies to yellow-green crystals, which melts at about 65° C.

2.6 parts of the above-mentioned nitration product are gradually introduced into 10 parts of a 66% solution of stannous chloride of 60° C. in concentrated hydrochloric acid. A tin-double salt precipitates at once which is sucked off. From this salt the 3-amino compound of the 2-methoxy-4-methoxymethyl-quinaldine is set free by means of concentrated sodium hydroxide solution and shaken out with methylenechloride. When worked up in the usual way this amino compound is obtained as slightly yellowish viscous oil which boils at 160° C. under 0.4 mm. pressure. On storing the oil slowly solidifies to crystals.

1 part of the amino compound mentioned above is suspended in 250 parts of water containing ¼ part of barium hydroxide, and gradually heated, while permanently cooling with ice, with a solution of 3 parts of barium permanganate in 250 parts of water. Thereupon the mixture is heated for a short time, sucked off while hot from manganese dioxide, the manganese dioxide is several times extracted with boiling water and the united filtrates are concentrated to ¼ of their volume under reduced pressure. The concentrated solution is shaken out with methylenechloride, the barium ions are now precipitated from the aqueous solution by the addition of the required quantity of sulfuric acid as barium sulfate. The filtrate from the barium sulfate precipitate is evaporated to dryness under reduced pressure. The 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5,6-dicarboxylic acid is obtained after rubbing on with acetone and filtration with suction as a yellow powder which readily dissolves in water. The aqueous solution of this dicarboxylic acid yields a strong red coloration with ferrous sulfate. On heating carbon dioxide is split off and 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5)-carboxylic acid (melting at 134° C.) is obtained. This methylester boils under 3 mms. pressure at 135° C. the methylesterchloride melts at 129° C. (from alcohol).

1 part of 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5)-carboxylic acid is treated with 3 parts of thionylchloride. The substance dissolves with the evolution of gas and while heating. After ½ hour's standing at room temperature the excess thionylchloride is evaporated under reduced pressure. The residue is covered by pouring with 10 parts of concentrated aqueous ammoniacal solution. One part of the carboxylic acid amide formed precipitates thereby. The whole mixture is evaporated under reduced pressure and the solid amide residue is extracted several times with warm methylenechloride. After the evaporation of the methylenechloride the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5)-carboxylic acid amide is obtained in crystals melting at 130° C.

1 part of this amide is boiled under reflux with 5 parts of phosphorus oxychloride. After a short time the amide has dissolved. It is still boiled for a short time and thereupon the phosphorus oxychloride is evaporated under reduced pressure. The residue is treated with ice and extracted with ether. After the

addition of ammonia until it reacts alkaline. The ethereal solution is dried by potassium carbonate, the ether is evaporated and the residue is distilled. There 2-methyl-3-methoxy-4-methoxymethyl-5-cyanopyridine distils under 0.01 mm. pressure as a colorless oil at a heating-bath temperature of 80–90° C.

I claim:

1. The process which comprises treating a 2-alkoxy-quinaldine-4-carboxylic acid derivative of the group consisting of carboxylic acid halide and ester derivatives with ammonia to form the 2-alkoxy-quinaldine-4-carboxylic acid amide, converting the latter into the corresponding 4-nitrile by the action of a dehydrating agent, transforming the 4-nitrile into a 4-aminomethyl-quinaldine by the action of a hydrogenating agent, acting upon the 4-aminomethyl compound with nitrous acid, esterifying the hydroxyl group of the 4-methoxy-4-hydroxymethyl-quinaldine formed in the condensation manner, nitrating the 2-alkoxy-4-acyloxymethyl-quinaldine by treatment with nitric acid, reducing the nitro compound obtained to the corresponding amino compound by the action of a reducing agent, converting the amino compound by the action of an oxidizing agent into a 2-methyl-3-alkoxy-4-acyloxymethyl-pyridine-5-carboxylic acid, esterified at the carboxylic group in 5-position by acid treatment, transforming the 5-carboxylic group into the 5-carboxylic acid halide group in the manner known per se, acting upon the 2-methyl-3-alkoxy-4-acyloxymethyl-pyridine-5-carboxylic acid halide with ammonia and converting the 5-carboxylic-alkoxy-4-(3-alkoxymethyl-pyridine-5-carboxylic acid amide into a 2-methyl-3-alkoxy-4-acyloxymethyl-pyridine-5-nitrile by the action of a dehydrating agent.

2. The process which comprises treating a 2-methoxy-quinaldine-4-carboxylic acid chloride with ammonia to form the 2-methoxy-quinaldine-4-carboxylic acid amide, converting the latter into the corresponding 4-nitrile by the action of phosphorous oxychloride, transforming the 4-nitrile by the action of sodium and alcohol into the 4-aminomethyl-quinaldine, acting upon the 4-aminomethyl compound with nitrous acid, esterifying the hydroxyl group of the 4-methoxy-4-hydroxymethyl-quinaldine formed by diazotization with acetic anhydride, nitrating the 2-methoxy-4-acetoxymethyl-quinaldine by treatment with nitric acid, reducing the nitro compound obtained by the action of

amino compound by the action of permanganate into 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5,6-dicarboxylic acid, splitting off the carboxylic group in 6-position by heat treatment, transforming the 5-carboxylic group into the 5-carboxylic acid chloride group by treatment with thionylchloride, acting upon the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid chloride with ammonia and converting the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-carboxylic acid amide into the 2-methyl-3-methoxy-4-methoxymethyl-pyridine-5-nitril by the action of phosphorus oxychloride.

3. A compound of the formula

wherein X stands for a constituent of the group consisting of carboxylic, carboxylic acid halide, carboxylic acid amide and nitrile groups.

4. A compound of the formula

wherein X stands for a constituent of the group consisting of carboxylic, carboxylic acid halide, carboxylic acid amide and nitrile groups.

5. The compound of the formula

6. The compound of the formula

7. The compound of the formula

ARTHUR SALZER

Dieselben beginnen gegen 180° unter Röthung zu sintern, und schmelzen gegen 240° zu einer trüben Flüssigkeit, die beim weiteren Erhitzen zu einer gelblichen, undurchsichtigen Masse erstarrt, alsdann noch nicht bei 270° wieder schmilzt und sich von 260° ab braunroth färbt. Der zur Analyse bestimmte Antheil wurde durch Umkrystallisiren aus etwa 150 Theilen kochendem Wasser in haarfeinen, schwach gelblichen Nadeln erhalten und im Vacuum über Schwefelsäure getrocknet:

0.1763 g Sbst.: 0.4020 g CO_2, 0.0971 g H_2O. — 0.1863 g Sbst.: 0.4275 g CO_2, 0.0983 g H_2O. — 0.2019 g Sbst.: 0.4597 g CO_2, 0.103 g H_2O. — 0.2097 g Sbst.: 0.4779 g CO_2, 0.1111 g H_2O. — 0.1492 g Sbst.: 9.3 ccm N (16°, 764 mm). — 0.2155 g Sbst.: 13.9 ccm N (10°, 774 mm).

$C_{10}H_9NO_2 + H_2O$.

Ber. C 62.18, H 5.69, N 7.25.

Gef. » 62.18, 62.58, 62.10, 62.15, » 6.12, 5.86, 5.69, 5.89, » 7.16, 7.22.

Die Substanz ist:

Methyloxyisocarbostyril, $C_6H_4 \lt \begin{matrix} CO - NH \\ C(OH):C.CH_3 \end{matrix} + H_2O$;

sie löst sich nicht in verdünntem Ammoniak, leicht in fixen Alkalien mit gelber Farbe, wird daraus durch verdünnte Säuren oder Salmiak wieder niedergeschlagen und ziemlich leicht von heissem Alkohol aufgenommen.

Zur Bestimmung des Krystallwassers wurde die Substanz im Vacuum auf 100° bis zur Gewichtsconstanz erhitzt:

0.4341 g Sbst. verloren 0.0406 g.

$C_{10}H_9NO_2 + H_2O$. Ber. H_2O 9.33. Gef. H_2O 9.39.

Da die bei dieser Bestimmung hinterbliebene wasserfreie Substanz sich durch die lang andauernde Erhitzung ziemlich stark verfärbt hatte, wurde eine Portion der Substanz bei niedrigerer Temperatur entwässert und zwar wie folgt: durch Kochen von 1 g Substanz mit 60 ccm Xylol so lange, bis sich im Halse des Kolbens nicht mehr Wassertropfen condensirten. Der Körper war dabei nicht in Lösung gegangen und völlig farblos geworden. Nach dem Absaugen und Waschen mit Benzol wurde er bei 100° getrocknet.

0.1615 g Sbst.: 0.4091 g CO_2, 0.0788 g H_2O. — 0.2050 g Sbst.: 13.9 ccm N (16°, 768 mm).

$C_{10}H_9NO_2$. Ber. C 68.57, H 5.14, N 8.00.

Gef. » 69.09, » 5.42, » 7.98.

Die wasserfreie Substanz löst sich in siedendem Aethylbenzoat und scheidet sich daraus, wenn nur sehr kurze Zeit erhitzt worden ist, in derben Nadeln wieder ab, die aber, wie ihre gelbe Farbe verräth, bereits Zersetzungsproducte enthalten. Länger andauerndes Kochen mit Aethylbenzoat zersetzt die Substanz völlig.

[illegible] Der vorliegende Methyläther wird durch [illegible]stündiges Kochen [illegible] starker Salzsäure nicht merklich verändert, dagegen durch Sieden mit Jodwasserstoffsäure (Sdp. 127°) unter Entwickelung von Jodmethyl in [illegible]-1-Oxychlorisochinolin zurückverwandelt, welches an seiner Alkalilöslichkeit und durch den Schmelzpunkt (191° statt 195°) erkannt wurde.

[illegible] Reducirt man das Oxychlorisochinolin (0.4 g) mit Jodwasserstoffsäure vom Sdp. 127° (3 ccm) und rothem Phosphor (0.2 g) im Rohr durch [illegible]stündiges Erhitzen auf 200°, so liefert die entstandene klare Flüssigkeit nach dem Uebersättigen mit Alkali und Abblasen mit Dampf ein stark alkalisch reagirendes Destillat, welches Tetrahydroisochinolin enthält; diese Base wurde an dem Schmelzpunkt des Chlorhydrates (193—194° statt 195—197°) und an dem des Chloroplatinats (ca. 220° unter Zerfall statt 231—232°) erkannt.

II. α-Phtalimidopropionsäureester und Natriummethylat.

Zur Darstellung des Esters werden je 100 g Phtalimidkalium und [illegible]-Brompropionsäureester in einem Erlenmeyer-Kolben tüchtig verrührt und dann im Oelbade auf 150—160° so lange (ca. [illegible] Stunden) unter [illegible] Durchmischen erhitzt, bis das Product einen durch[illegible] Syrup darstellt. Dann rührt man es noch vor [illegible] Erkalten in [illegible] Wasser ein, wobei das Bromkalium sich [illegible] und die neue Verbindung als dickes Oel (ca. 80 g) [illegible] ungelöst [illegible] nach dem Erkalten erstarrte und getrocknete Substanz wird mit etwa 1½ L Ligroin ausgekocht, welches die Verunreinigungen [illegible] und beim Abkühlen den

α-Phtalimidopropionsäureester, $C_8H_4O_2N.CH(CH_3).CO_2C_2H_5$, [illegible] Krystallen vom Schmp. 61—63° abscheidet; Ausbeute [illegible] g, d. h. ca. 60 pCt. der Theorie.

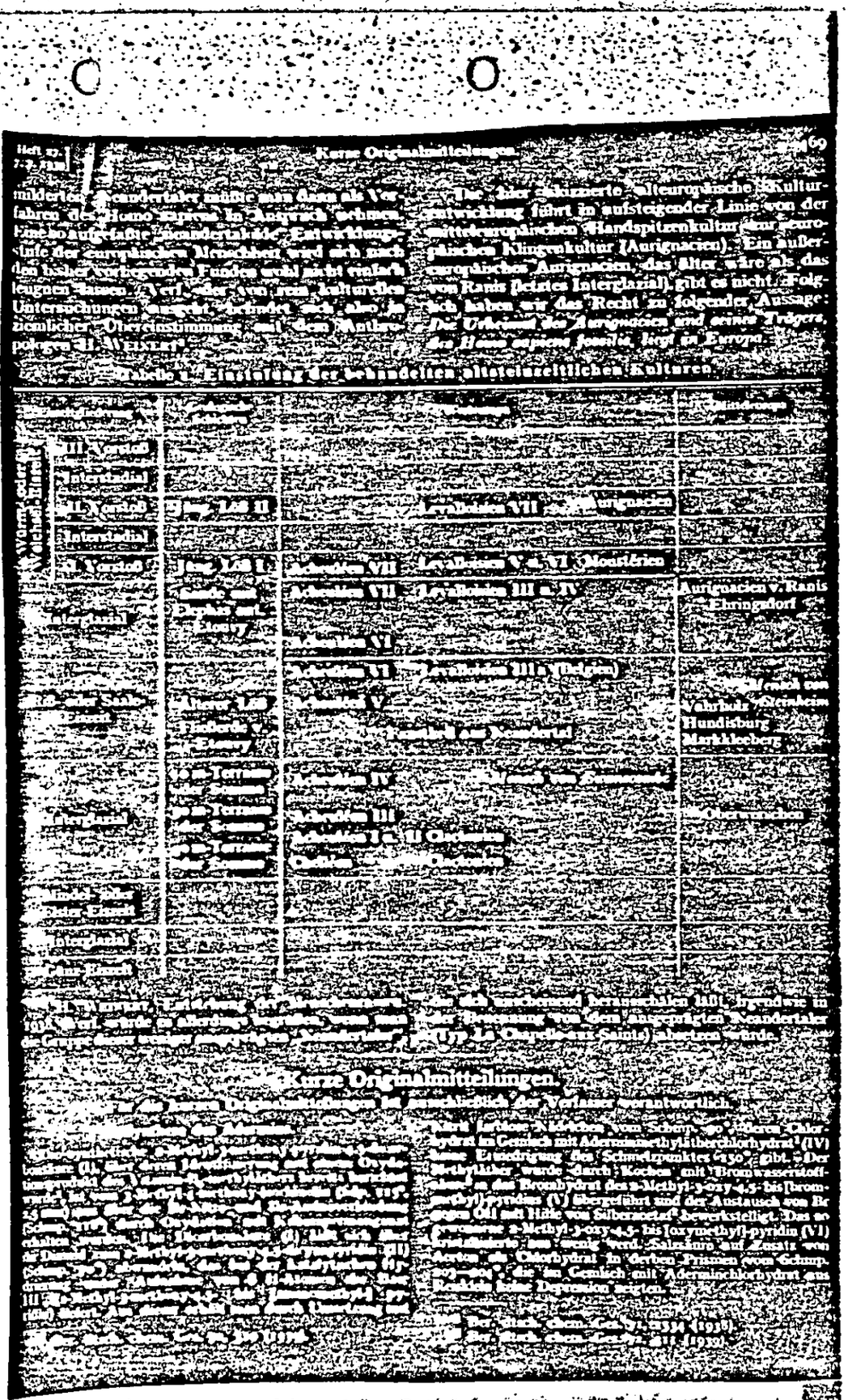
[illegible] 0.1[illegible]60 g Sbst.: [illegible] ccm N ([illegible]°, 752 mm). — 0.1856 g Sbst.: 0.4536 g CO_2, [illegible] g H_2O.

$C_{13}H_{13}NO_4$. Ber. C 63.16, H 5.26, N 5.67.

Gef. » [illegible], » [illegible], » 5.60.

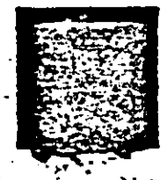
Der Ester löst sich leicht in den üblichen Lösungsmitteln, wenig in kochendem Wasser und kaltem Ligroin.

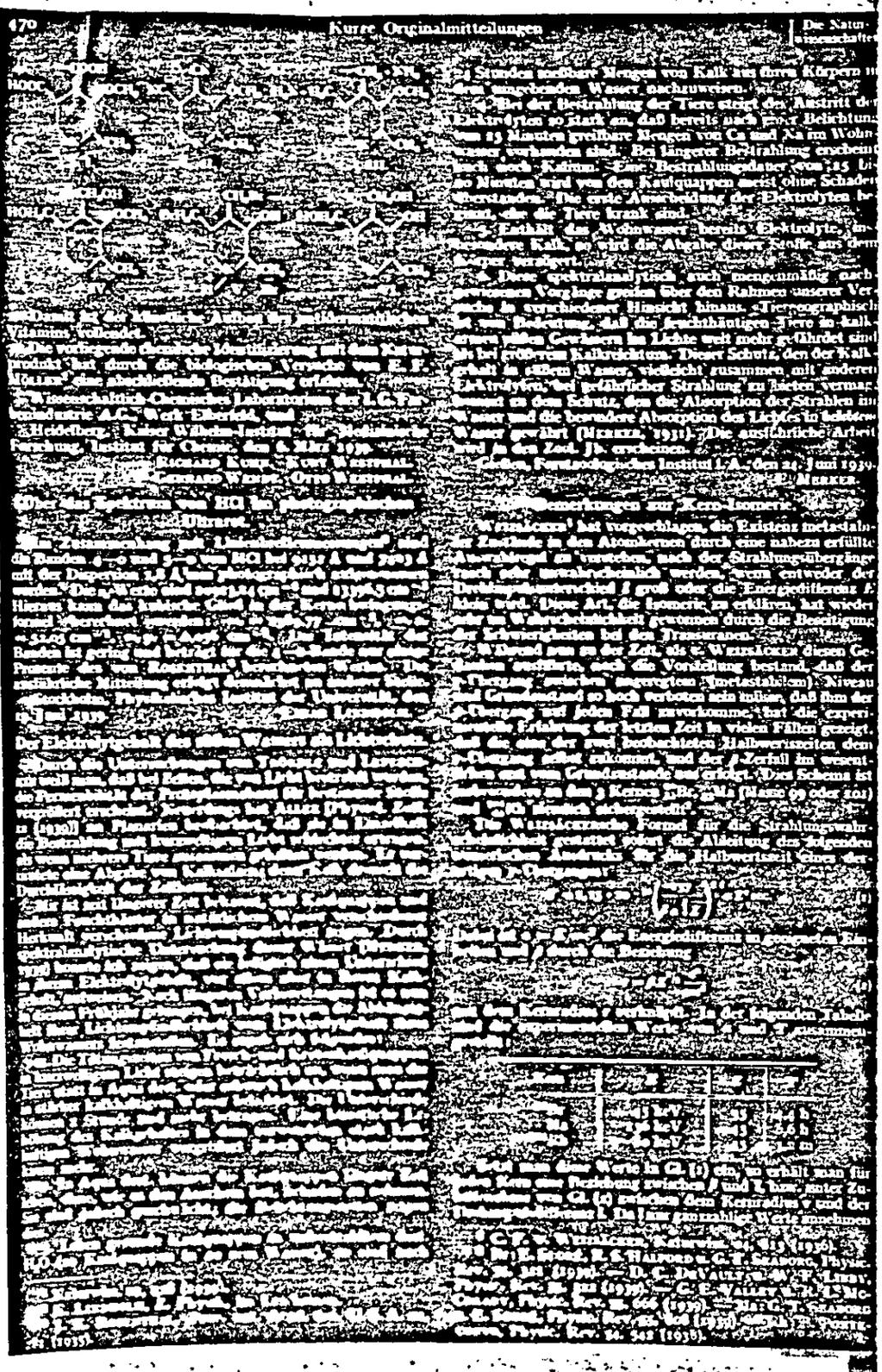
[illegible] Umsetzung mit Natriummethylat nahmen wir wie folgt vor. [illegible] g Ester in 12 ccm Holzgeist werden mit einer Lösung von [illegible] g Natrium in 30 ccm Holzgeist 2 Stunden lang am Rückflusskühler gekocht, dann die grünlich-braune Flüssigkeit auf ein kleines Volumen eingeengt und darauf mit warmem Wasser vermischt. Die gelbe Lösung erstarrt, wenn man sie mit Salmiaklösung versetzt, zu einem Brei farbloser Krystalle (ca. [illegible] g).



Kurze Originalmitteilungen.

Für die Kurzen Originalmitteilungen ist nur der Verfasser verantwortlich.





96. Richard Kuhn und Gerhard Wendt: Über die funktionellen Gruppen des Adermins

(Aus d. Kaiser Wilhelm-Institut für medizin. Forschung, Heidelberg, Institut für Chemie.)

(Eingegangen am 18. Mai 1938.)

Die Einwirkung von Diazomethan auf Vitamin-B_6-chlorhydrat führt zu einer Verbindung $C_9H_{13}O_3N$, die aus Chloroform auf Zusatz von Petroläther in farblosen Prismen vom Schmp. 90° krystallisiert. Dieses Derivat gibt im Gegensatz zum Vitamin keine Farbreaktion mit Eisenchlorid und kuppelt auch nicht mit diazotierter Sulfanilsäure. Mit Jodwasserstoffsäure wird schon unter den Bedingungen der Methoxylbestimmung 1 Mol. Methyljodid abgespalten. Es liegt also ein Monomethyläther der Vitamin-B_6-Base $C_8H_{11}O_3N$ vor, der als Adermin-methyläther bezeichnet werden soll. Die weitere Behandlung mit Essigsäure-anhydrid in Pyridin liefert einen Diacetyl-adermin-methyläther $C_{13}H_{17}O_5N$ vom Schmp. 54°, dessen in Exalton und in Campher bestimmte Schmelzpunktserniedrigung die einfache Molekulargröße bestätigt. Die angeführten Derivate zeigen, daß alle 3 Sauerstoffatome des Adermins Hydroxylgruppen angehören, eine davon ist enolisch (ebenolisch), die zwei anderen sind alkoholisch. Am Diacetyl-adermin-methyläther läßt sich auch bei erhöhter Temperatur kein aktives Wasserstoffatom mehr nachweisen. Das N-Atom des Vitamins ist offenbar ringtertiär.

Beschreibung der Versuche.

Adermin-methyläther: Eine Lösung von 300 mg B_6-Chlorhydrat in 10 ccm Methanol wird in kleinen Mengen mit einer ätherischen Diazomethan-Lösung bis zum Aufhören der Stickstoffentwicklung versetzt, danach fügt man einen kleinen Überschuß Diazomethan zu und läßt einige Stunden bei Zimmertemperatur stehen. Nach dem Abdampfen des Lösungsmittels wird der Rückstand in 12 ccm Chloroform gelöst, die Chloroformlösung schüttelt man 2-mal mit 1–2 ccm Wasser aus. Die wäßrige Lösung wird im Vak. zur Trockne gedampft und der Rückstand unter 10⁻² mm destilliert. Bei 110–120° (Außentemp.) destilliert ein schwach gelb gefärbtes Öl über, das schon während der Destillation teilweise erstarrt. 130 mg Destillat. Nach dem Umkrystallisieren aus Chloroform-Petroläther (Sdp. 30–50°) erhält man schneeweiße, zu Drusen vereinigte Nadeln vom Schmp. 89,5–90°.

[illegible] bei 20° getrocknet.

[illegible] mg Subst. gaben mit CO_2 2,30 mg H_2O 1,216 mg Subst. 0,287 ccm N_2 [illegible] ccm Ard

$C_9H_{13}O_3N$ (183,1) [illegible] C 58,96 H 7,16 N 7,65 CH_3 8,21

[illegible] 7,88 7,37 [illegible] (Methoxyl)

[illegible] 1,83 mg Subst. in 0,3 ccm Pyridin

[illegible] 1,83 mg Subst. CH_3 CH_3, α_D = 0,46° CH_3

[illegible] 0,30°

[illegible] 0,3 ccm Pyridin

[illegible] 1,63 mg Subst. CH_3 CH_3, α_D = 0,44° CH_3

[illegible] 0,30°

Diacetyl-adermin-methyläther: 130 mg Adermin-methyläther [illegible] ccm über Bariumoxyd getrocknetem Pyridin in der Kälte gelöst und mit 2 ccm destilliertem Essigsäure-anhydrid versetzt. Die Lösung blieb 18 Stdn. bei etwa 20° stehen, wobei sie sich gelb färbte. Darnach wurde 20 Min. auf dem Dampfbad erwärmt. Nach dem Erkalten [illegible] das gleiche Volumen

absol. reiner Alkohol angesetzt und die Lösung im Vak. zur Trockne gedampft. Der Rückstand war ein dickflüssiges Öl, das unter 10^{-3} mm bei 95—100° (Luftbad) destillierte und beim Reiben sofort erstarrte. Ausb. 67 mg (92% d. Th.). Schmp. 53—54° (klar).

[illegible] 4.760 mg Sbst.: 7.80 mg CO_2, 2.10 mg H_2O. — [illegible] mg Sbst.: 0.234 ccm N_2 ([illegible]°, 748 mm). — [illegible] mg Sbst.: [illegible] ccm [illegible]-NaOH (alkalisch verseift mit [illegible] NaOH (30 Min. erhitzt)).

[illegible] (307.3). Ber. C [illegible], H 6.42, N [illegible], Acetyl 32.22.
Gef. „ [illegible], „ [illegible], „ [illegible], „ [illegible].46.

Molekulargewichtsbestimmung nach Rast:
[illegible] 0.334 mg Sbst. in 4.160 mg Borneol (K = [illegible]): Δ = 7.6°. — [illegible] mg Sbst. in 3.347 mg Campher (K = 39): Δ = 16.5°.
[illegible] 267. Gef. 238 (Borneol), 231 (Campher).

Zerewitinoff-Roth: 0.422 mg Sbst.: [illegible] = 0.00 ccm CH_4 (20°)
[illegible] = 0.17 [illegible] (75°).

257. Richard Kuhn und Leonhard Birkofer: Zur Theorie der Mutarotation; die Mutarotation und katalytische Hydrierung der Gly-[illegible]oside sekundärer Amine.

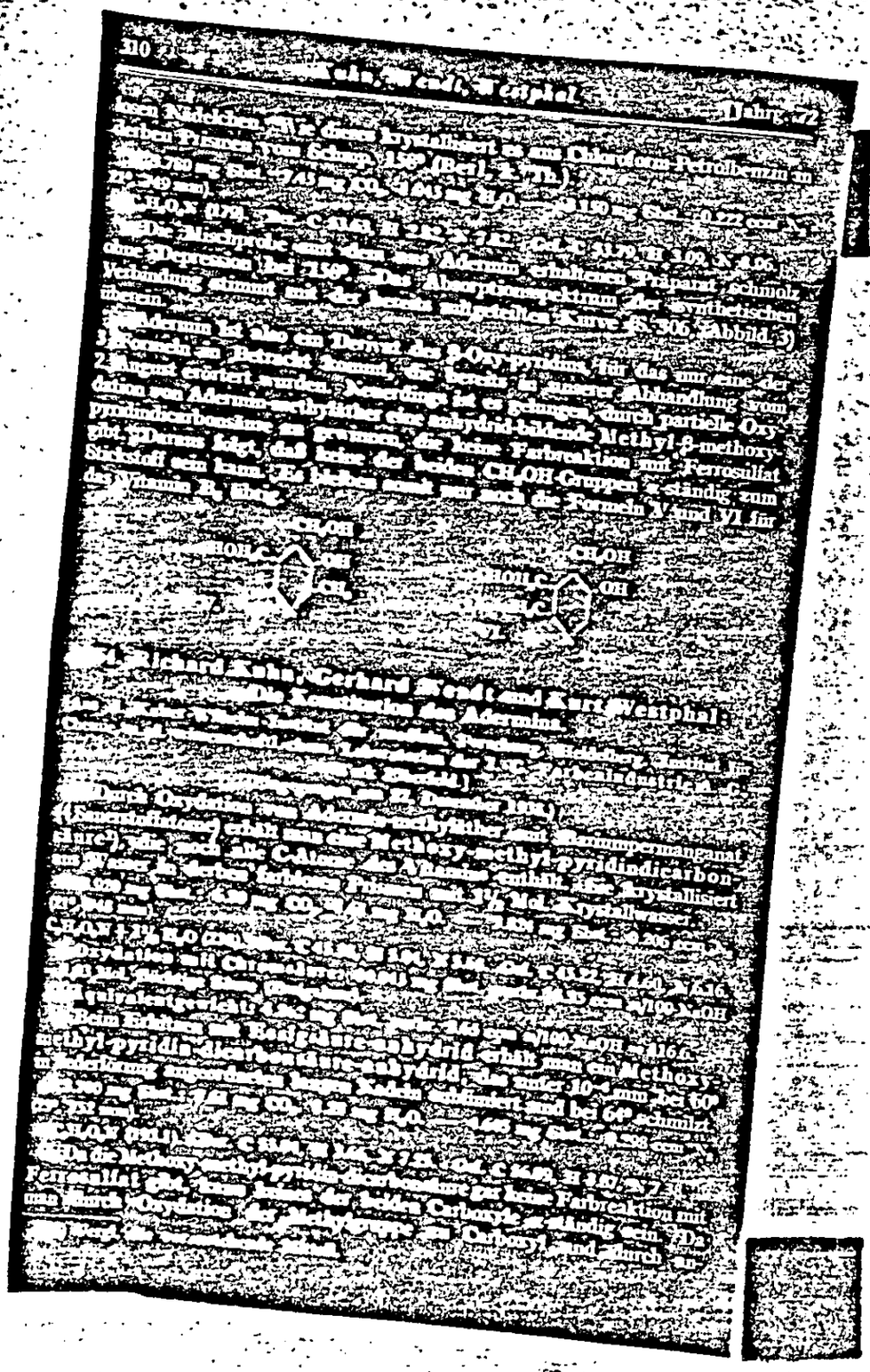
[Aus d. Kaiser-Wilhelm-Institut für medizin. Forschung, Heidelberg, Institut für Chemie.]

(Eingegangen am 22. Juni 1938.)

Die von Dubrunfaut[1]) 1846 entdeckte Mutarotation der Glucose ist in der Folgezeit bekanntlich bei allen reduzierenden Zuckern und vielen ihrer Derivate festgestellt worden. Die Ursache der Drehungsänderung wird seit der Auffindung der β-Glucose durch C. Tanret[2]) allgemein in der Einstellung eines echten Gleichgewichts zwischen den, nach B. Tollens[3]) ringförmig gebauten, α- und β-Formen erblickt.

Viele Forscher haben versucht, die Erscheinung durch vorübergehende Anlagerung und Wiederabspaltung von Wasser zu erklären, so C. S. Hudson[4]), T. M. Lowry[5]), E. F. Armstrong[6]), J. C. Irvine und E. S. Steele[7]) u. a. Aber all diese Vorstellungen scheinen heute hauptsächlich aus folgenden beiden Gründen verlassen zu sein. Einerseits haben J. W. Baker, Ch. K. Ingold und J. F. Thorpe[8]) in einer sorgfältigen Untersuchung über die Mutarotation der Tetramethylglucose in absolut wasserfreiem Methanol gezeigt, daß die Reaktionsgeschwindigkeit vom Zusatz steigender Wassermengen unabhängig ist, und daraus den Schluß gezogen, „that the mutarotation of sugars is essentially a tautomeric phenomenon, and that neither analytical nor subanalytical traces of water intervene in the manner suggested by Lowry and Armstrong's hypotheses". Andererseits haben R. Kuhn

1) Compt. rend. Acad. Sciences 23, 38 (1846).
2) Bull. Soc. chim. France [3] 13, 728 (1895). [illegible] B. 16, 922 (1883); [illegible]
4) Journ. Amer. chem. Soc. [illegible] (1910); [illegible] J. Dillis, Rec. Trav. chim. Pays-Bas [illegible] (1929); [illegible] 922 (1927); R. Kuhn
[illegible] Jacob, [illegible] Chem. 113, 389 (1924).
5) Journ. chem. Soc. London [illegible], 1316 (1903).
6) Journ. chem. Soc. London [illegible], 1305 (1903).
7) Journ. chem. Soc. London 107, 1230 (1915).
8) Journ. chem. Soc. London 125, 268 (1924).



schließende Abspaltung von CO_2 zur 3-Methoxy-pyridin-dicarbonsäure-(4.5)[1]) gelangt, bleiben für die Methoxy-methyl-dicarbonsäure nur die Formulierungen I und II übrig.

[illegible] ist nun auf einem synthetischen Wege, über den an anderer Stelle näher berichtet werden wird, gelungen, die 2-Methyl-3-methoxy-pyridin-dicarbonsäure-(4.5) (II) zu gewinnen. Ihr Anhydrid sublimiert unter 10⁻⁴ mm bei 60° in farblosen Nadeln vom Schmp. 64°.

[illegible] 725 mg Sbst.: 7.70 mg CO_2, 1.25 mg H_2O.

[illegible] $C_{9}H_{7}O_{4}N$ (193.1). Ber. C 55.96, H 3.66. Gef. C 55.92, H 3.66.

Oxydation [illegible] Chromsäure: [illegible] 8.44 mg Sbst. verbr. [illegible] 53 ccm [illegible] NaOH [illegible] 92 Mol. Essigsäure.

Diese Substanz gibt mit dem entsprechenden Oxydationsprodukt des Adermins (Schmp. 64°) keine Depression. Für das Adermin ist damit die Formel III des 3-Oxy-4.5-di-[oxymethyl]-2-methyl-pyridins [illegible] wiesen.

III.

55. Richard Kuhn und Gerhard Wendt: Rückverwandlung von Adermin-methyläther in Adermin.

[Aus d. Kaiser-Wilhelm-Institut für Medizin. Forschung, Heidelberg, Institut für Chemie.]

(Eingegangen am 27. Dezember 1938.)

Bei der Einwirkung von Bromwasserstoffsäure auf den Methyläther des Adermins (I) wird nicht nur die Methoxygruppe verseift, sondern überdies in beiden Oxymethylgruppen OH gegen Br ausgetauscht. Man erhält in guter Ausbeute eine Verbindung $C_{8}H_{10}ONBr_{3}$ vom Schmp. 217°, die das Bromhydrat des 2-Methyl-3-oxy-4.5-di-[brommethyl]-pyridins (II) darstellt. Die Umsetzung dieses Tribromkörpers mit 3 Mol. Silberacetat in wäßriger Lösung führt zum freien Vitamin B_6 (III) zurück.

Beschreibung der Versuche.

Spaltung des Adermin-methyläthers mit Bromwasserstoffsäure.

[illegible] 00 mg Adermin-methyläther (I) werden in 5 ccm 66-proz. Bromwasserstoffsäure 15 Min. zum Sieden erhitzt. Während des Erkaltens scheidet sich der Bromkörper II in schwach gelben, derben, zu Drusen vereinigten Krystallen ab. Ausb. 206 mg (75% d. Th.). Durch Umlösen aus

wenig siedendem Wasser erhält man die Substanz in farblosen Spießen. Schmp. 217° (Zers.).

Zur Analyse wurde 1 Stde. im Hochvakuum bei 20° getrocknet. 3.820 mg Sbst.: 3.52 mg CO_2, 1.00 mg H_2O. — 8.324 mg Sbst.: 0.173 ccm N_2 (19°, 761 mm). — 1.617 mg Sbst.: 2.429 mg AgBr.

$C_8H_{10}ON_2Br_3$ (375.9). Ber. C 25.14, H 2.68, N 7.72, Br 63.79.
Gef. „ 25.11, „ 2.91, „ 8.84, „ 63.92.

Die Substanz gibt mit dem Phenolreagens von Folin-Denis eine tiefblaue Farbreaktion und kuppelt mit diazotierter Sulfanilsäure unter Bildung eines orangefarbigen Azokörpers.

Umsetzung mit Silberacetat.

195 mg Tribrom-Körper (II) werden in 20 ccm Wasser 15 Min. zum Sieden erhitzt. Nach dem Erkalten fügt man langsam eine wäßrige Lösung von 312 mg Silberacetat in 60 ccm Wasser zu. Nach dem Zentrifugieren und Waschen der Silberfällung wird in das Filtrat H_2S eingeleitet. Die wäßrige Lösung wird unter Zusatz von 2-n. HCl zur Trockne gedampft. Die Ausbeute an Adermin-chlorhydrat ist nahezu quantitativ (102 mg).

Die Krystalle werden 2-mal mit Aceton gewaschen und aus wenig Wasser unter Zusatz von Aceton u. a. umkrystallisiert. Schmp. 200—201°. Die Mischprobe gibt keine Depression.

Zur Analyse wurde 1 Stde. bei 20° im Hochvakuum getrocknet.
3.690 mg Sbst.: 6.33 mg CO_2, 1.86 mg H_2O. — 4.942 mg Sbst.: 0.279 ccm N_2 (20°, 762 mm).

$C_8H_{11}O_3N.HCl$ (205.6). Ber. C 46.69, H 5.88, N 6.81. Gef. C 46.81, H 5.79, N 6.71.

Vitamin-B_6-Base (III).

Eine Lösung von 200 mg B_6-Chlorhydrat in 10 ccm Wasser wird tropfenweise mit einer wäßrigen Lösung von 162 mg Ag-Acetat in 10 ccm Wasser versetzt. Von dem ausgeschiedenen Silberchlorid wird abfiltriert. Das Filtrat wird durch Einleiten von H_2S von Ag befreit.

Nach dem Eindampfen erhält man 81 mg weiße Krystalle, die bei 130° unter 10^{-4} mm sublimieren. Aus Aceton farblose Nadeln vom Schmp. 159°. J. C. Keresztesy und J. R. Stevens[4]) hatten den Schmp. 160° gefunden.

Zur Analyse wurde 3-mal aus Aceton umkrystallisiert und 1 Stde. im Hochvakuum bei 20° getrocknet.
3.715 mg Sbst.: 7.73 mg CO_2, 2.18 mg H_2O. — 4.321 mg Sbst.: 0.302 ccm N_2 (22°, 758 mm).

$C_8H_{11}O_3N$ (169.1). Ber. C 56.77, H 6.56, N 8.28. Gef. C 56.73, H 6.57, N 8.22.

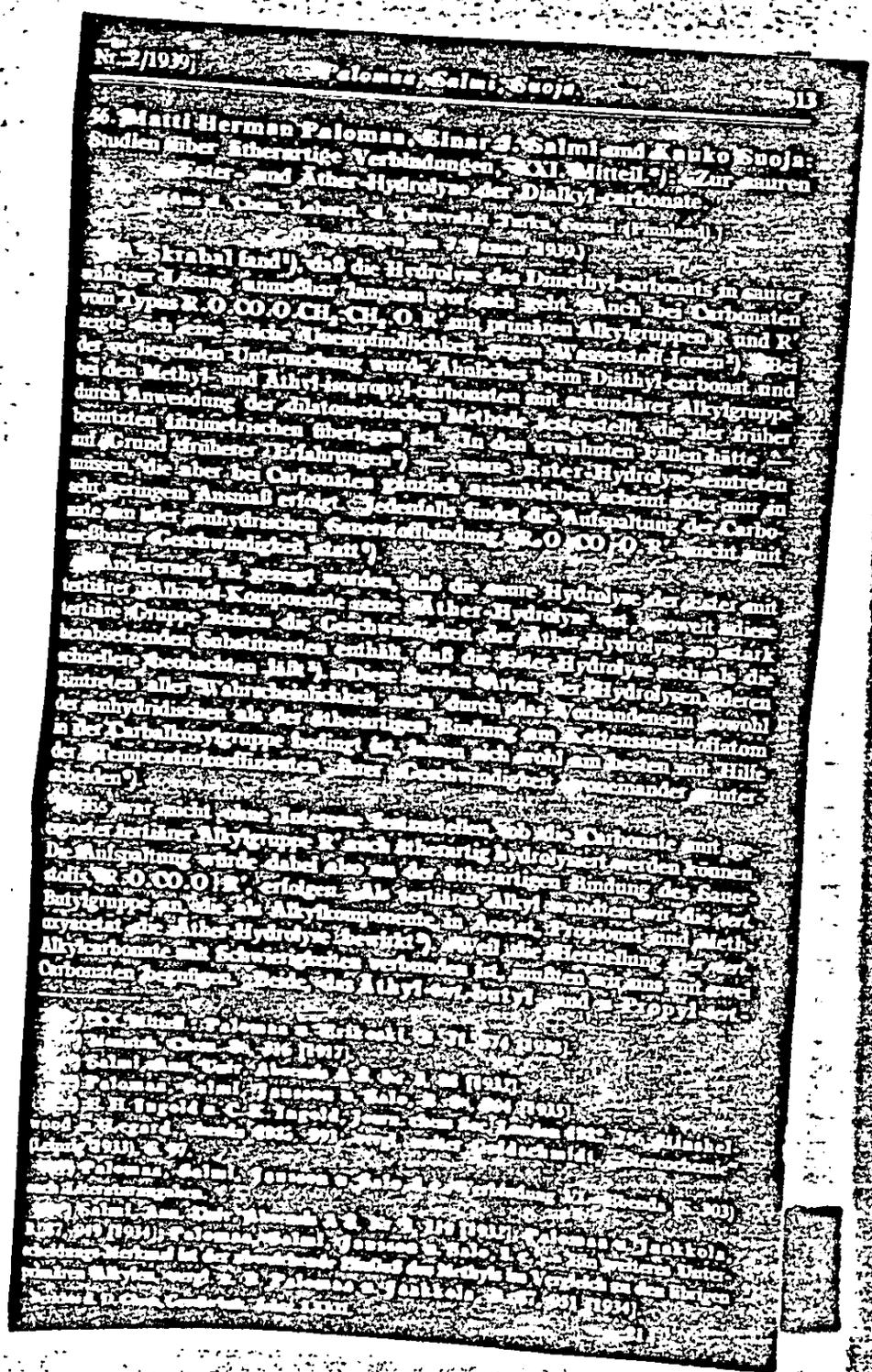
Adermin-bromhydrat.

[illegible] mg B_6-Base werden in verd. Bromwasserstoffsäure gelöst und im Vak. zur Trockne gedampft. Das Bromhydrat erhält man aus Wasser auf Zusatz von Aceton in derben, oft zu Drusen vereinigten farblosen Nadeln oder Doppelpyramiden, die bei 1[illegible]° unter Zers. schmelzen.

3.933 mg Sbst.: 5.57 mg CO_2, 1.71 mg H_2O. — 3.941 mg Sbst.: 0.176 ccm N_2 (22°, [illegible] mm). — 4.041 mg Sbst.: [illegible] mg AgBr.

$C_8H_{12}O_3NBr$ (250.1). Ber. C 38.40, H 4.84, N 5.60, Br 31.97.
Gef. „ [illegible], „ [illegible], „ [illegible], „ 31.76.

[4]) J. [illegible] [1938].



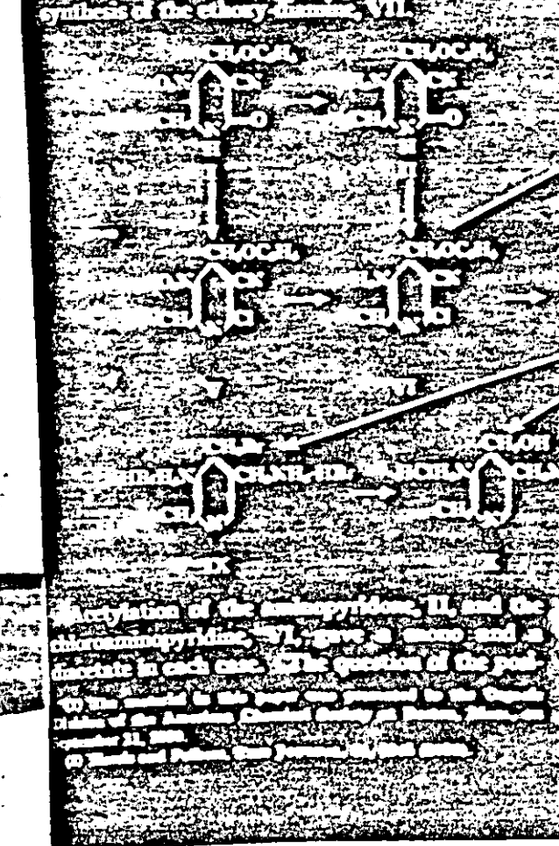
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Synthesis of Vitamin B_6. II

By STANLEY A. HARRIS AND KARL FOLKERS

In a previous article[1] a complete synthesis of vitamin B_6 was described. The present paper describes some variations and improvements in this synthesis, along with new derivatives of some of the intermediate compounds. These variations are shown in the set of reactions I → XII. The original synthesis is represented by the reactions I → V → VI → VII → VIII → XII → XI. The nitropyridone, I, was prepared by the nitration of 2-cyano-4-ethoxymethyl-6-methyl-2-pyridone, which in turn was prepared by the condensation of ethoxyacetylacetone and cyanoacetamide.

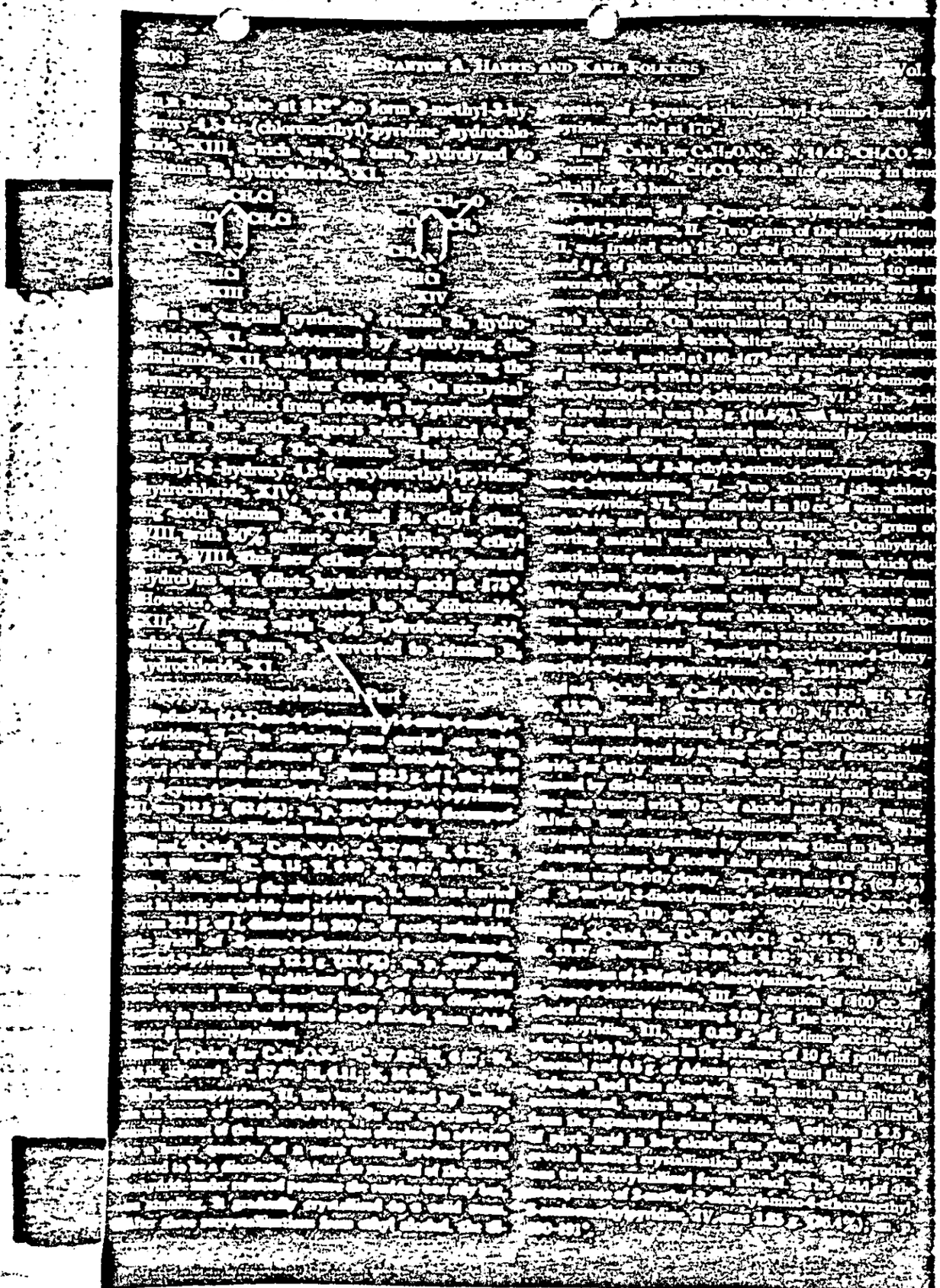
The ethoxy diamine, VII, is the key compound in all these syntheses. It has compound was prepared by two new variations of these reactions: I → II → VI → VII and I → II → VI → VIII → IV → VII. These variations are limited by the low yield in reaction II → VI. Compounds III and IV are not essential to the success of the synthesis of the ethoxy diamine, VII.

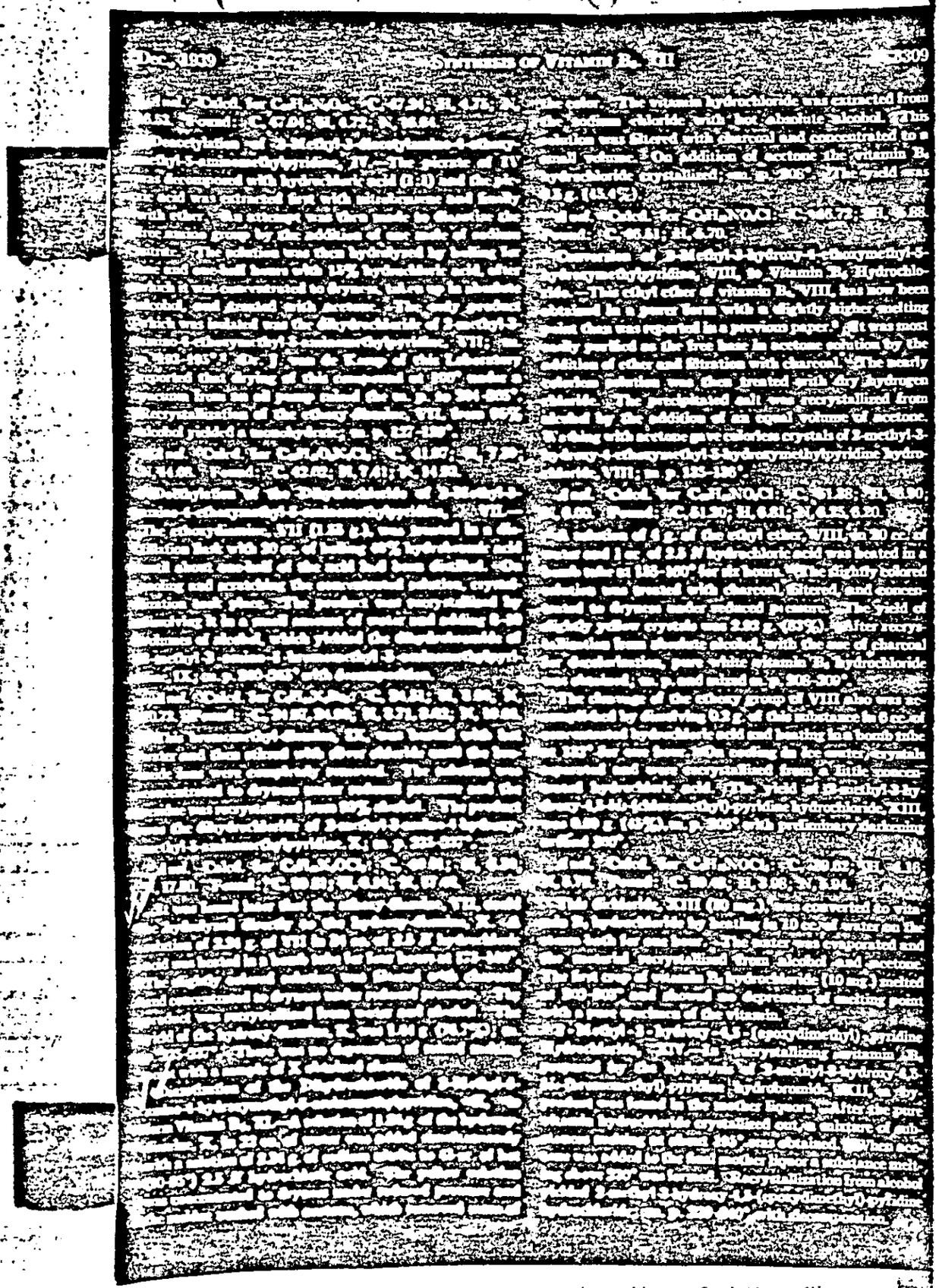


Acylation of the aminopyridone, II, and the corresponding aminopyridine, VI, gave, in each case, two products in each case. The question of the position of the acyl group in the diacetate of the aminopyridone, II, was settled only by analogy. Since the chloro-aminopyridine, VI, also formed a diacetate and the original pyridone, namely, 2-cyano-4-ethoxymethyl-6-methyl-2-pyridone, did not form an acetate when boiled with acetic anhydride, it was deduced that the diacetate of II had both acetyl radicals attached to the amino group.

The important variations in the synthesis start with the ethoxy diamine, VII. The first variation is represented by the reactions VII → VIII → XI. It was found that the ethoxy group of VIII could be split with dilute hydrochloric acid in a bomb tube reaction at 150°. This reaction eliminated the use of constant boiling hydrobromic acid and the necessity for the subsequent hydrolysis of the intermediate dibromide, XII. A second variation is shown by the steps VII → IX → X → XI. These steps also were shortened by another bomb tube reaction to give the third and most practical series of reactions, VII → X → XI. The ethoxy diamine, X, was more easily isolated and recrystallized than was the methoxymethyl derivative, VIII, of vitamin B_6.

The ethoxymethyl derivative, VIII, also was readily cyclized with concentrated hydrochloric acid





Acknowledgment.—The authors are indebted to Messrs. D. F. Hayman and W. Ross for the microanalyses and to Mr. A. N. Wilson for technical assistance.

Summary

Variations and improvements in the synthesis of vitamin B_6 have been made. The compounds 3-methyl-5-hydroxy-4-chloromethyl-6-hydroxymethylpyridine and 3-methyl-5-amino-4-chloromethylpyridine have been hydrolyzed directly to the corresponding dihydroxy derivatives by heating with dilute hydrochloric acid at 150–175° under pressure. Derivatives of some of the intermediates and of the ether and vitamin B_6 have been described.

Received December 10, 1939

[Contribution from the Department of Chemistry, Vassar College, and the School of Chemistry of the University of Minnesota]

The Reaction between 2,3-Dimethyl-1,4-naphthoquinone and Phenylmagnesium Bromide. II

By H. Marjorie Crawford

The structures of the two di-addition products ... established as shown by the following equa...

benzoic acid. The 10% compound was also formed by the reaction of phenyllithium on ether. The 10% monoöxo-addition compound of the original quinone, phenylmagnesium bromide and acid with the 10% monoöxo addition compound to give the 20% compound.

Starting with these two addition products, parallel series of reactions led to the same reduction products.

The decomposition and rearrangement of III to the formation of the 1% compound (II) and the unaltered ketone (I) by acetic acid, phenyllithium and phenylmagnesium bromide indicated that the formation of II from I involved the shift of one phenyl group from a carbon bearing the two to a carbon bearing a methyl group. Only small amounts of II were available and the only other reactions investigated were those with phenyllithium and with phenylmagnesium bromide in both of these reactions, decomposition of the metallic product with acid led to the formation of the hydrocarbon (IV). Careful decomposition of the metallic compound with water gave an intermediate carbinol (III), which, in the presence of acid, easily lost a molecule of water and gave the hydrocarbon. The hydrocarbon was difficult to oxidize with ordinary oxidizing agents, but was attacked readily by ozone to give formaldehyde and a ketone (V). When the ketone was treated with methylmagnesium iodide followed by acid, the hydrocarbon was formed again, so no rearrangement occurred during the reaction with ozone. Ozonization of the ketone (V) gave a known keto acid (VI). The structure of this known keto acid located the three phenyl groups in the hydrocarbon (IV) and in the ketone (V). The same hydrocarbon (IV) was obtained by starting with the 10% addition product (VII) and carrying out the same series of reactions. Dehydration of VII gave the 85% compound (VIII) which was extremely unreactive. VIII was recovered unchanged after attempts at oxidation with potassium dichromate and chromium trioxide in glacial acetic acid, with basic potassium permanganate, with hydrogen peroxide and with ozone. The only reactions which VIII could be made to undergo were reduction with zinc and acetic acid (which gave small amounts of two reduction products) and the reaction with organo-metallic reagents. When phenylmagnesium bromide or phenyllithium was added to VIII and the metallic compound was decomposed with acid, the hydrocarbon (IV) resulted, but if ammonium chloride was used for the decomposition, an intermediate carbinol (IX) could be isolated. Both ozonization and oxidation with potassium

minutes, with ammonium chloride and water, the ether extract gave 90% yields of the carbinol (IX).

Other analytical data on this compound are contained in the earlier paper[4] in which this compound was numbered (VIII).

1-Oxy-2,3-dimethyl-1,1,4-triphenyldihydronaphthalene, IX, m. p. 154°.—This carbinol was formed in 90% yields by the addition of phenylmagnesium bromide to VIII. It is very unstable in the presence of acid and when an alcohol solution of the carbinol was treated with hydrochloric acid, a molecule of water was lost with the formation of the hydrocarbon (IV). IX melts at 154° with the loss of a molecule of water and the formation of the hydrocarbon (IV). Warming with zinc chloride and concd. hydrochloric acid in benzene also converted IX to the hydrocarbon (IV). The Grignard machine showed one active hydrogen. Boiling for one hour with potassium permanganate and potassium hydroxide gave 90% of unchanged material. Boiling for one hour with potassium dichromate in glacial acetic acid gave a solid from which, after many recrystallizations from alcohol and ethyl acetate, it was possible to isolate a small amount of the 235° hydrocarbon. Ozonization of IX in chloroform gave the ketone (V), so dehydration to the hydrocarbon (IV) probably occurred before the reaction with ozone.

Anal. Calcd. for $C_{30}H_{26}O$: C, 89.51; H, 6.51. Found: C, 89.21, 88.95; H, 6.80, 6.75.

The 235° Hydrocarbon.—This compound, isomeric with the 150° hydrocarbon (IV), was formed in small amounts in many attempts to oxidize the hydrocarbon (IV) with potassium dichromate or potassium permanganate in glacial acetic acid or with ozone, and to oxidize the carbinol (IX) with potassium dichromate in glacial acetic acid.

Heating the hydrocarbon (IV) with acetic acid alone or with iodine in acetic acid did not convert it into the higher melting isomer. Ozone converted 0.4 g. of the 235°-compound into an oil from which no solid material could be obtained. The 235° compound was only slightly soluble in alcohol and in ethyl acetate, but could be crystallized from benzene.

Anal. Calcd. for $C_{30}H_{24}$ (384.2): C, 93.71; H, 6.29. Found: C, 93.84, 93.23; H, 6.29, 6.07; mol. wt. (camphor), 360.

The author wishes to thank the University of Minnesota for the courtesy shown her as an Honorary Fellow of the University while on leave from Vassar College in the spring of 1938.

Summary

Starting with the two di-addition products from the reaction between phenylmagnesium bromide and 2,3-dimethyl-1,4-naphthoquinone, parallel series of reactions lead to the same product, a hydrocarbon.

Structures have been assigned to these two di-addition products, to the two compounds resulting from the dehydration and rearrangement of these compounds, and to four new compounds obtained in these series of reactions.

POUGHKEEPSIE, N. Y. RECEIVED AUGUST 24, 1939

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXXVI. Oxidation and Reduction Products of Equilenin

BY RUSSELL E. MARKER AND EWALD ROHRMANN

In previous work from this Laboratory[1] it was observed that equilenin when reduced with Adams catalyst in acidic ethanol gave approximately a 70% yield of $\Delta^{5,7,9}$-estratrienol-17. No other reduction products were isolated. Ruzicka, Müller and Mörgeli[2] in a somewhat similar reduction obtained this same product in addition to some α-dihydroequilenin. By modifying the reduction technique these workers were able to obtain a $\Delta^{5,7,9}$-estratrienediol-3,17 which was identical with one of the diols obtained by the reduction of equilenin with sodium.[3,4]

When the hydrogenation of equilenin is carried out in a neutral medium with Adams catalyst, the essential product is α-dihydroequilenin, a product first isolated from the phenolic fraction of mares pregnancy urine by Wintersteiner and co-workers[5] and later prepared by Marker and co-workers[1] by the reduction of equilenin with aluminum isopropylate. The hydrogenation of α-dihydroequilenin in acidic ethanol yields the same $\Delta^{5,7,9}$-estratrienol-17 as was obtained from equilenin, indicating that the hydroxyl group at C-17 is of the α-configuration.

In a previous comprehensive investigation of the carbinol fraction of mares pregnancy urine[6] we reported the isolation from the chromic anhy-

(1) Marker, Kamm, Oakwood and Laucius, THIS JOURNAL, 59, [illegible] (1937).

(2) Ruzicka, Müller and Mörgeli, Helv. Chim. Acta, 21, [illegible] (1938).

(3) Marker, Rohrmann, [illegible] and [illegible], THIS JOURNAL, [illegible] (1938).

(4) David, [illegible] (1938).

(5) Wintersteiner, Schwenk, Hirschmann and Whitman, THIS JOURNAL, 58, 2652 (1936).

(6) Marker and Rohrmann, THIS JOURNAL, 61, [illegible] (1939).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

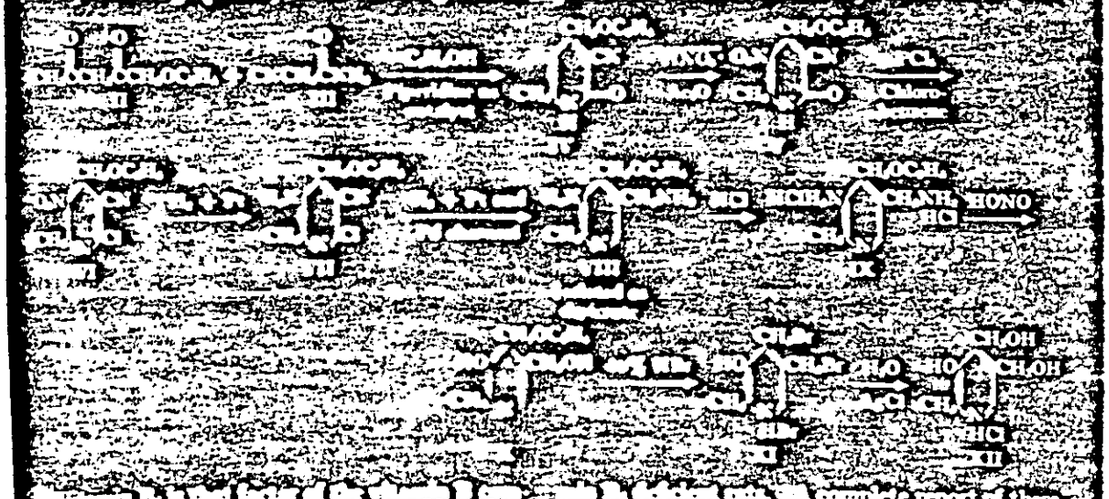
Synthesis of Vitamin B_{12}

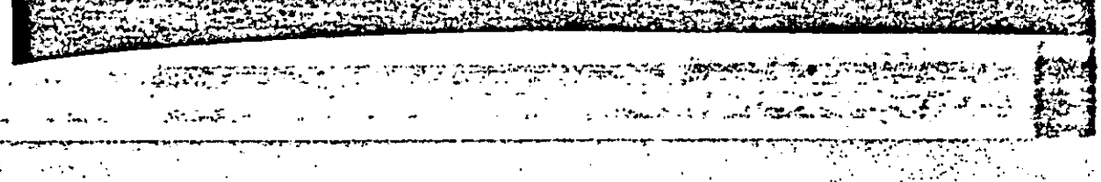
BY D. M. BONNER, J. A. ZOSKE AND KARL FOLKERS

The synthesis of vitamin B_{12} has been fully described in the preceding [illegible] (5,6-Dimethyl-1-α-D-ribofuranosyl-benzimidazolyl)-cobamide, by the researchers described in the accompanying two papers from this Laboratory,[1] and also by the second three papers of Rimington and his co-workers.[2]

The complete synthesis of the vitamin B_{12} has been accomplished also, and the authors recently reported that the synthetic vitamin B_{12} cyanochloride is chemically identical with the natural vitamin B_{12} hydrochloride, and that it is biologically active.

The paper describing the basis of the synthesis and the synthesis of vitamin B_{12} and other cobalt derivatives is presented by [illegible]



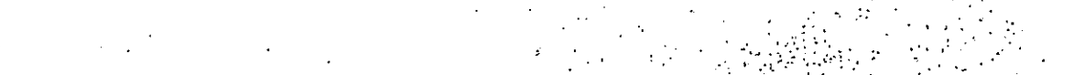


vitamin B_{12} not only produces a cure of the deficiency but also a stimulation of growth.[3] It also has been found that a severe macrocytic hypochromic anemia developed in puppies when the anti-dermatitis factor (vitamin B_6) was apparently the only missing component of the diet. This anemia was cured by the addition of this factor to the diet.[4] A biological relationship between vitamin B_{12} and unsaturated fatty acids also has been studied, and recently Birch[5] revealed that the physiological function of vitamin B_{12} is connected with the utilization of the unsaturated fatty acids.

The biological assay of the synthetic vitamin which was performed in the Merck Institute for Therapeutic Research by Dr. R. J. Reedman confirmed the results previously reported by Rimington and Stevens[2] for the natural vitamin [illegible] a single dose of 100 gamma effecting a complete cure within fourteen days when fed to rats

[illegible] complete report of these [illegible] preparation of vita-

Experimental Part



Received March 11, 1939

Chemical Compounds as Flotation Reagents. II

By C. C. Bozorth and Frances von Bruenchenhein

Koones for their assistance in the preparation of the vitamin B_6 used in this work.

Summary

1. The methyl ether of vitamin B_6 was oxidized to give a lactone $C_9H_9O_3N$ and a dibasic acid $C_9H_9O_5N$.

2. The acid was shown to be 2-methyl-3-methoxypyridine-4,5-dicarboxylic acid.

3. Vitamin B_6 was shown to be 2-methyl-3-hydroxy-4,5-di-(hydroxymethyl)-pyridine.

RAHWAY, NEW JERSEY RECEIVED MARCH 15, 1939

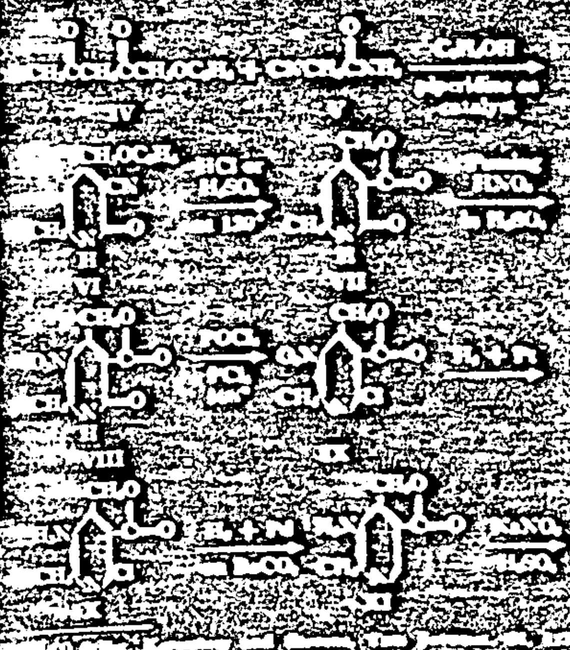
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Structure of Vitamin B_6. II

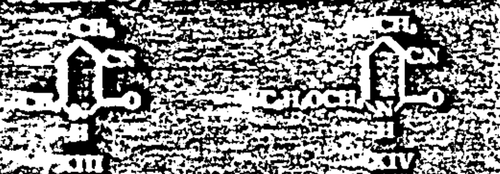
BY STANTON A. HARRIS, ERIC T. STILLER AND KARL FOLKERS

This paper deals with the syntheses of the dibasic acid $C_9H_9O_5N$, I, and the lactone $C_9H_9O_3N$, II, which were obtained by Stiller, Keresztesy and Stevens[1] by the oxidation of the methyl ether of vitamin B_6. The synthetic lactone and acid were

found to be identical with the corresponding compounds obtained from vitamin B_6. Thus, conclusive proof is furnished that vitamin B_6 is 2-methyl-3-hydroxy-4,5-di-(hydroxymethyl)-pyridine, III. The syntheses may be represented graphically in the following manner.



The synthesis of VI is similar to the synthesis of 3-cyano-4,6-dimethyl-2-pyridone, XIII, which was obtained by the condensation of acetylacetone



and cyanacetamide as previously described by Bardhan,[2] and also Simonsen and Nyak.[3]

The condensation of IV and V might have led to the alternative 3-cyano-4-methyl-6-ethoxymethyl-2-pyridone, XIV. The proof that the condensation product had structure VI, instead of XIV, was shown by its conversion on hydrolysis to the lactone VII, which was obtained in 65% yield. It is obvious that the pyridone derivative, XIV, would be incapable of giving a lactone on hydrolysis. The pyridone derivative, VI, was obtained pure in better than 80% yield with no evidence of any other product being formed.

Experimental Part

3-Cyano-4-ethoxymethyl-6-methyl-2-pyridone, VI.—To 68.3 g. of cyanoacetamide,[4] V, dissolved in 800 cc. of hot 95% alcohol, 93.1 g. of ethoxyacetylacetone[5] and ca. 8.5 cc.

(1) Stiller, Keresztesy and Stevens, [illegible] (1939).

(2) Bardhan, *J. Chem. Soc.*, 2223 (1929).

(3) Simonsen and Nyak, *ibid.*, 107, 792 (1915).

(4) Corson, Scott, and Vose, "Org. Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1932, p. 173.

(5) Sommelet, *Bull. soc. chim.*, [4] 1, 382 (1907).

of piperidine were added with shaking, whence the mixture became warm, as it was necessary to heat the solution. Crystals soon appeared. The mixture was allowed to stand overnight, cooled and filtered. The product was washed with 95% alcohol. The yield of white crystals was 22 g. or 81%, m. p. 209–210° corr. The product was purified by crystallization from boiling 95% alcohol; m. p. 210°.

Anal. Calcd. for $C_8H_8ON_2$: C, 62.50; H, 5.25; N, 14.58. Found: C, 62.33; H, 5.19; N, 14.80.

The Lactone of 3-Carboxy-4-hydroxymethyl-6-methyl-2-pyridone, VII.—Fifteen grams of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone was mixed with 125 cc. of concentrated hydrochloric acid and heated at 120–125° for four hours. The reaction mixture was then poured into 400 cc. of water and ice mixture, whereupon the lactone of 3-carboxy-4-hydroxymethyl-6-methyl-2-pyridone, VII, crystallized. It was filtered, washed with water and the dried product weighed 11.1 g. or 87%. The product was recrystallized from water; m. p. above 320°.

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.24; N, 8.48. Found: C, 58.14, 57.90; H, 4.19, 4.19; N, 8.46.

The following method was used later and was found to be preferable. A solution of 98 g. of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone, VI, in 1120 cc. of 50% sulfuric acid was refluxed for three hours. The temperature of the liquid was 120°. The reaction mixture was then poured into 3.5–4.0 liters of water and placed in the ice room overnight. On the following day, the crystals were filtered and washed well with water, alcohol and ether, and dried at a moderate temperature, 85–90°. The yield of VII was 70.5 g. or 88.5%.

The Lactone of 3-Carboxy-4-hydroxymethyl-5-nitro-6-methyl-2-pyridone, VIII.—A solution of 98 g. of the lactone of 3-carboxy-4-hydroxymethyl-6-methyl-2-pyridone, VII, in 62 cc. of concentrated sulfuric acid was added to an ice-cold mixture of 124 cc. of concentrated sulfuric acid and 82 cc. of fuming nitric acid (sp. gr. 1.5). The mixture warmed spontaneously to a temperature of 35 to 45°. After the temperature had started to fall the mixture was cooled to 35° and poured onto crushed ice. The final volume was about one liter. A yellow solid formed immediately which was filtered and dried at 65°. The yield of the lactone of 3-carboxy-4-hydroxymethyl-5-nitro-6-methyl-2-pyridone was 99.8 g. or 83.5%. On recrystallization from water it melted at 270–280° with decomposition.

Anal. Calcd. for $C_8H_6N_2O_5$: C, 45.71; H, 2.86; N, 13.33. Found: C, 45.82; H, 2.92; N, 13.21.

The Lactone of 2-Methyl-3-nitro-4-hydroxymethyl-5-carboxy-6-chloropyridine, IX.—About 183 g. of the lactone of 3-carboxy-4-hydroxymethyl-6-methyl-2-pyridone, VIII, 300 cc. of phosphorus oxychloride and 765 g. of phosphorus pentachloride were mixed and refluxed until a solution resulted (three-quarters of an hour). The phosphorus oxychloride was distilled off under reduced pressure, the solid separated, ground with ice and water, filtered, washed with water, and the product precipitated by adding petroleum ether (B. p. 60–68°) to the solution of 2-methyl-3-nitro-4-hydroxymethyl-5-carboxy-6-chloropyridine in [illegible]. The product was recrystallized from benzene or ethyl acetate; m. p. 176–178°.

Anal. Calcd. for $C_8H_5N_2O_5Cl$: C, 41.03; H, 2.19; N, 12.25. Found: C, 41.90; H, 2.10; N, 12.44.

The Lactone of 2-Methyl-3-amino-4-hydroxymethyl-5-carboxy-6-chloropyridine, X.—A solution of 11.3 g. of the lactone of 2-methyl-3-nitro-4-hydroxymethyl-5-carboxy-6-chloropyridine, IX, in 250 cc. of glacial acetic acid with 0.4 g. of platinum oxide catalyst was shaken with hydrogen at three atmospheres pressure until three moles had been absorbed. The solution was cooled, filtered and the crystalline precipitate well washed with ether. The last yield of the lactone of 2-methyl-3-amino-4-hydroxymethyl-5-carboxy-6-chloropyridine, X, was 8.7 g. or 87.7%. After recrystallization from alcohol, the m. p. was 280–282°.

Anal. Calcd. for $C_8H_7NO_3Cl$: C, 48.30; H, 3.53; N, 14.11. Found: C, 48.32; H, 3.46; N, 14.23.

The Lactone of 2-Methyl-3-amino-4-hydroxymethyl-5-carboxypyridine, XI.—A suspension of 5.95 g. of the lactone of 2-methyl-3-amino-4-hydroxymethyl-5-carboxy-6-chloropyridine, X, and 10 g. of 5% Pd-$BaCO_3$ catalyst in 250 cc. of absolute alcohol was shaken with hydrogen at three atmospheres pressure at 60°. The absorption of hydrogen was stopped after one mole had been used and on cooling, spontaneous crystallization of a chlorine-free compound took place. After recrystallization from alcohol, the m. p. was 222–226°. The yield of the lactone of 2-methyl-3-amino-4-hydroxymethyl-5-carboxypyridine, XI, was 4.2 g. or 87.5%.

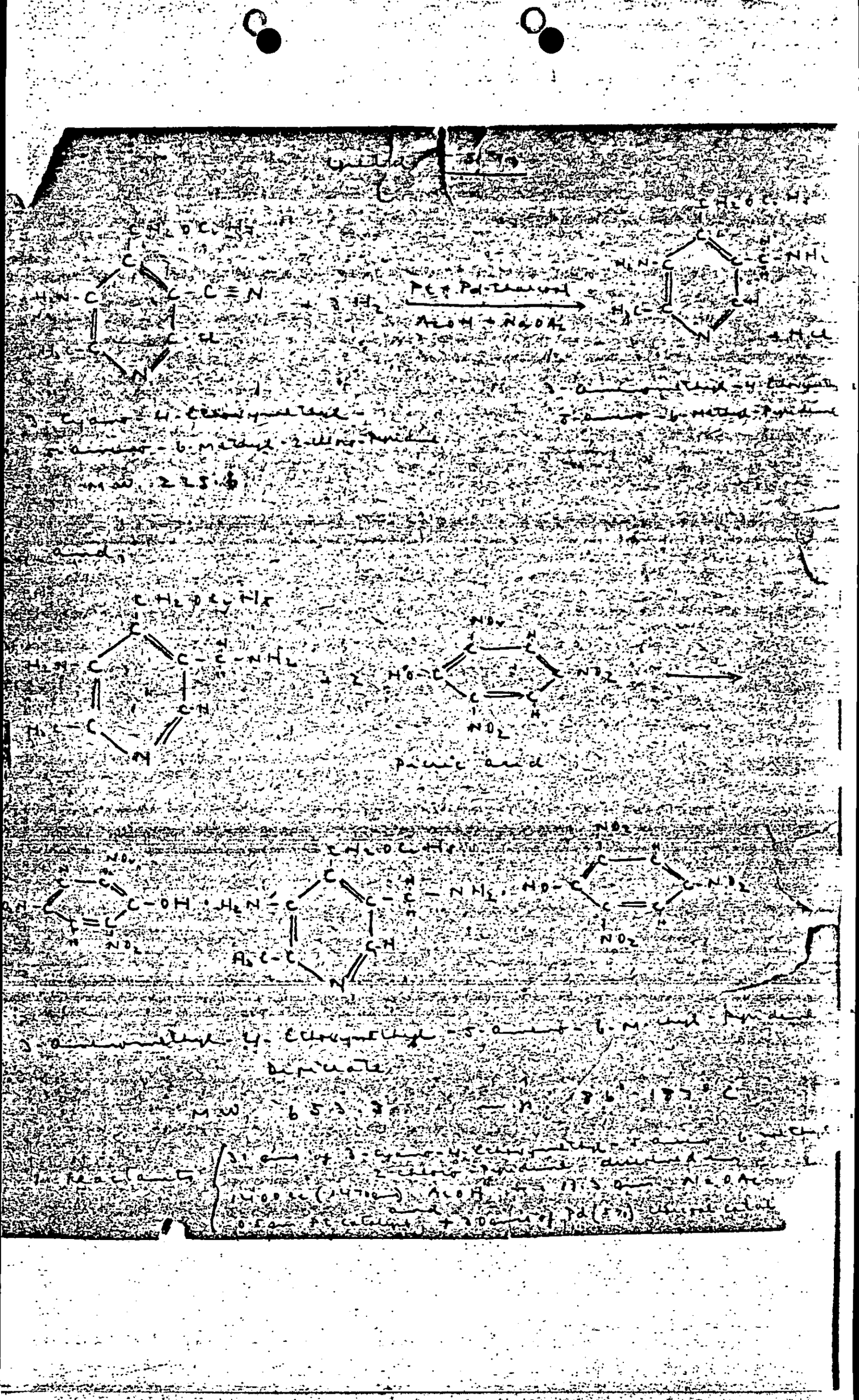
Anal. Calcd. for $C_8H_9NO_3$: C, 58.88; H, 5.56; N, 8.59. Found: C, 58.62; H, 5.78; N, 8.67.

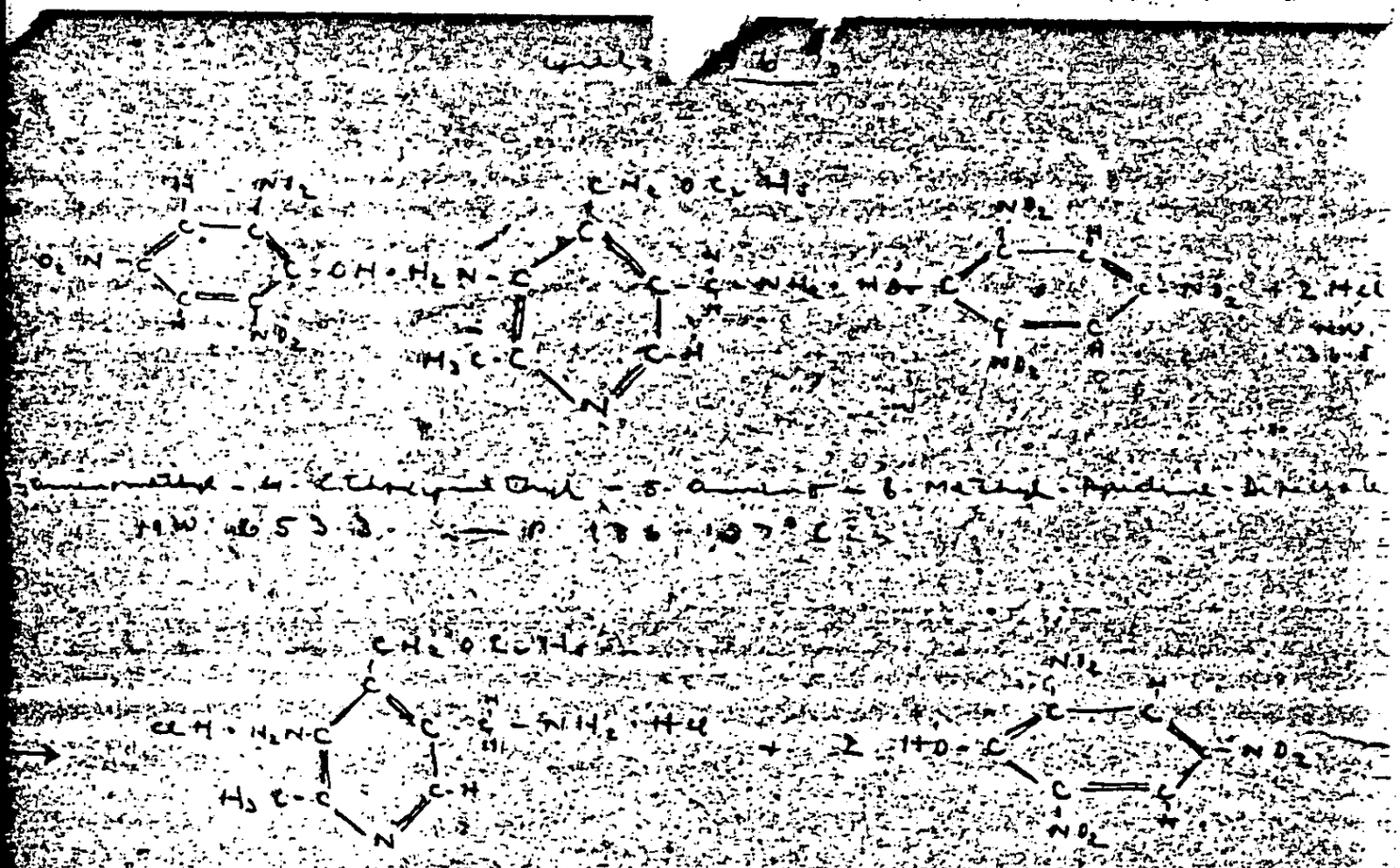
The aminopyridine derivative, XI, was also made directly from the nitropyridine derivative, IX, by dissolving 20.27 g. of the lactone of 2-methyl-3-nitro-4-hydroxymethyl-5-carboxy-6-chloropyridine, IX, in a mixture of 1 liter of ethyl acetate and 1 liter of 95% alcohol and shaking with hydrogen at the pressure of 0.75 g. of platinum oxide catalyst and 20 g. of 5% Pd-$BaCO_3$ catalyst. The first three moles of hydrogen was absorbed in fifteen minutes, whereupon [illegible] several hours to absorb the fourth mole. It was filtered from the catalyst, concentrated to dryness and recrystallized from water in the presence of charcoal. The [illegible] 5%; m. p. 220°.

The Picrate of the Lactone of 2-Methyl-3-amino-4-hydroxymethyl-5-carboxypyridine.—The above aminopyridine derivative, XI, may be isolated readily quantitatively as its picrate by adding an alcoholic solution of picric acid to an alcoholic solution of the amine. It was recrystallized from alcohol; m. p. 245–250°.

Anal. Calcd. for $C_{14}H_{11}O_{10}N_5$: C, 42.75; H, 2.80; N, 17.81. Found: C, 42.68; H, 2.62; N, 17.73.

The Lactone of 2-Methyl-3-hydroxy-4-hydroxymethyl-5-carboxypyridine, XII.—To 18.5 g. of the lactone of 2-methyl-3-amino-4-hydroxymethyl-5-carboxypyridine, XII, dissolved in 100 cc. of 25% sulfuric acid and cooled in ice, was added a slight excess of sodium nitrite (1 g. in 10 cc. of water). When this diazo solution was added slowly to 25 cc. of boiling 50% sulfuric acid solution. After the addition was complete, the solution was cooled and neutralized





2-aminomethyl-4-Chloromethyl-5-acetoxy-6-Methyl-Pyridine-Dihydrochloride
MW 265.3 — mp 178-180°C

6-Methyl-Pyridine-Dihydrochloride
MW 201 — mp 195°C

MW 229.1

1. Reactants { To 39 g of 2-aminomethyl-4-Chloromethyl-5-acetoxy-6-Methyl-Pyridine-Dihydrochloride
100 cc of 1:1 HCl (= 59 gms of 36% HCl)
No water added

2. Reflux for 1 hr at temp 50°C (122°F)

3. Cool the mixture to 25°C (77°F)

4. Extract the mixture with three 100 cc portions of N-Butanol (sp gr 1.2 ± 1.0 lbs/gal)

5. Extract the mixture with the top four 100 cc portions of ether (till the ether shows no more yellow color is withdrawn)

6. Concentrate the acid phase to a thick syrup —

Cumyl-acetic acid

Phenol

Filter the crude

Wash the crude with portions of H_2O

Recrystallize the crude from absolute alcohol

Cool the soln to 10° C crystals form

add 200 cc of H_2O and 200 cc of the

hot small portions add a slight excess

of 10% H_2SO_4

Filter out the $BaSO_4$

Wash the $BaSO_4$ with ether (3 x)

Evaporate the mixed solvents

Distill the Cumyl-acetic-acetone (at

15 mm) to get a liquid boiling at

[illegible]

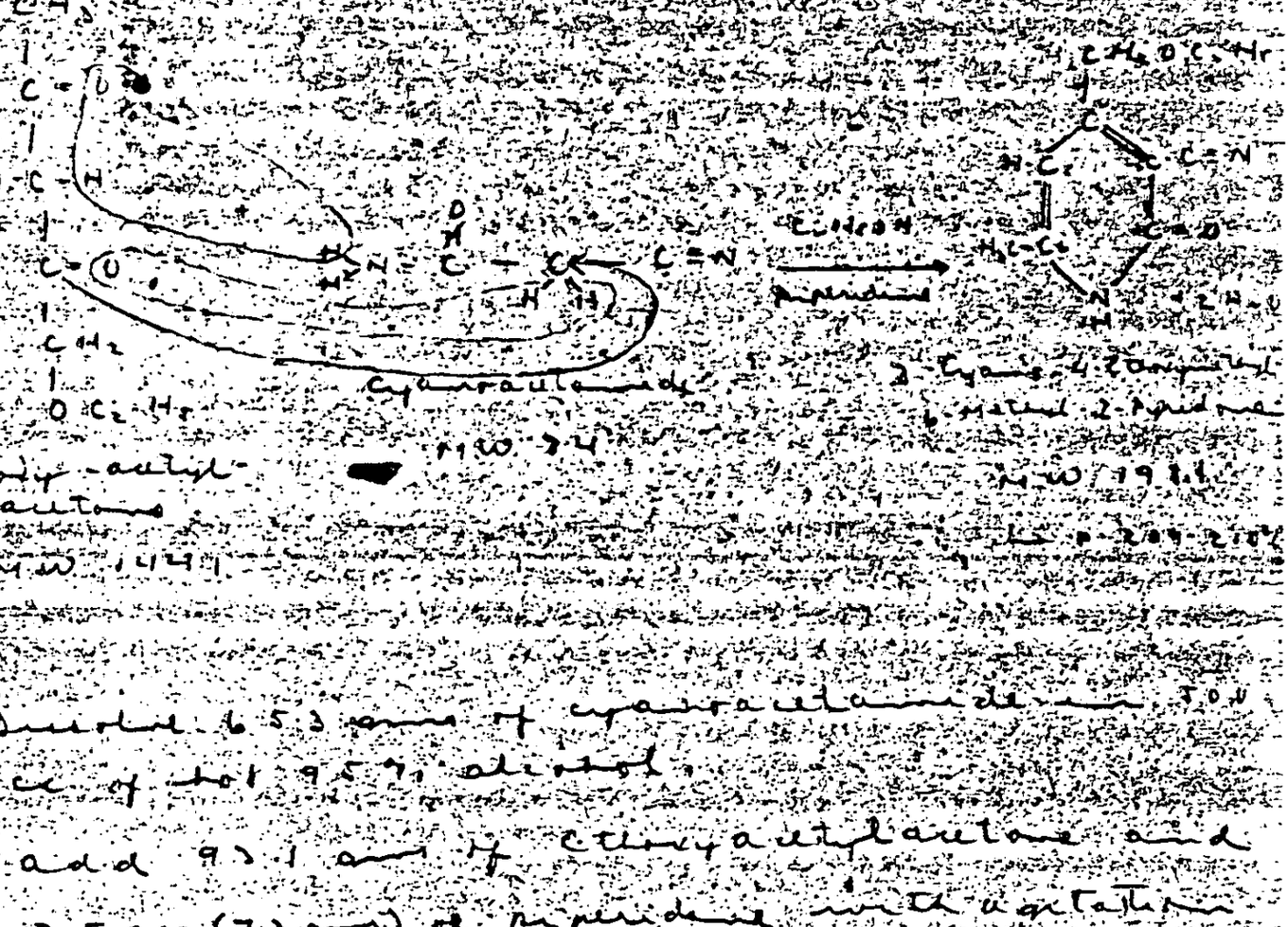
Yield 97 %

Ethyl cyano acetate — cyanoacetamide

M.W. 113.1 — M.W. 84.0

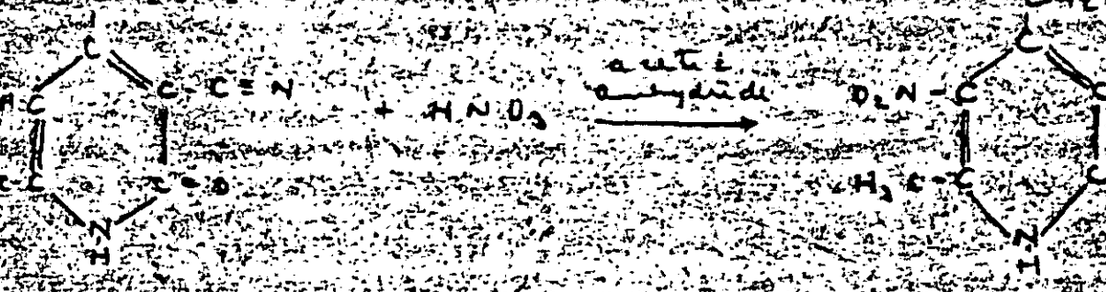
m.p. 119° - 120°C

1. From 4 moles of ethyl cyanoacetate
   to
   3½ L of conc. aqueous NH_3
   and
   acetate
2. When the addn. is complete (in about 3 hours),
   cool to −3°C (+ 12°F)
3. Filter the product.
4. Wash the product with two 5½ cc portions
   of −7°C ethyl alcohol
5. Dry in air
6. Dissolve in 450 cc of hot (75°C ≈ 167°F)
   ethyl alcohol
7. Cool to 10°C (50°F), crystals deposit
   quantitatively
8. Filter the crystals
9. Wash once with 5½ cc of −7°C ethyl alcohol
10. Dry in air



1. Dissolve 6.5 gms of cyanoacetamide in 30 cc of hot 95% alcohol.
2. Add 9.1 gms of ethyl acetoacetate and 8.5 cc (7.1 gms) of piperidine with agitation and cooling. Crystals soon appear. Keep the mixture at 25°C (77°F) for 12 hrs.
3. Filter the crystals.
4. Wash the crystals twice with 20.0 cc portions of 95% EtOH.
5. Dissolve the crystals in about 350 cc of boiling 95% EtOH.
6. Cool to 10°C to obtain a crop of pure crystals.
7. Filter the crystals.
8. Wash and with 20.0 cc of 10°C alcohol.
9. Dry the crystals.

Yield 32 %



3-Cyano-4-ethoxymethyl-6-Methyl-2-Pyridone

MW 194

3-Cyano-4-ethoxymethyl-5-Nitro-6-Methyl-2-Pyridone

MW 239

1. Dissolve 5 gms. of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone in 15 cc (11 gms) of Ac2O and cool to 0°C.
2. add { 2.2 cc. (3.3 gms) of fuming nitric acid dissolved in 2.0 cc (2.2 gms) of acetic anhydride } 9.2 gms mixed
3. The solid pyridone and dissolves and heat is evolved. When the temperature reaches 43°C (110°F.) cool the rxn to 25°C (77°F)
4. allow to stand till no further temperature rise is observable.
5. add 10 gms of water at 0°C and keep at 0°C till crystallization is complete
6. Filter the crystals
7. Wash twice with 5 cc portions of H2O at 0°C.
8. Dried the crystals in 20 cc (17 gms) of acetone (230)

9. Slowly add 2 cc of conc HCl (37% w/w) to precipitate the nitrophenol, stirring the soln at 5°C.

10. Filter the Nitrophenol crystals

11. Wash twice with three portions of water at 0°C

12. Dissolve the crystals in 25 cc of water at 50°C.

13. Cool the soln to 30°C

14. add 250 cc of petroleum ether to precipitate the Nitrophenol crystals.

15. Filter the crystals

16. Wash once with 5 cc of water at 0°C

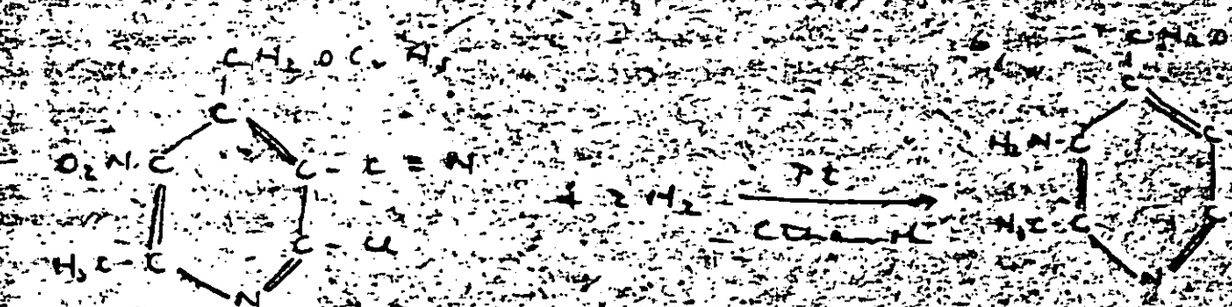
17. Dry the crystals

4. Cool the residue and add 100 cc of H_2O.
100 cc of 95% Ethanol.
5. Extract the aqueous mixture 10 times with
10 times with 100 cc (total) portions of
petroleum ether.
6. Concentrate the extract first at atmospheric
pressure (to removal of the solvent)
and then at a vacuum of 1 mm.
This is done in order to remove the last
traces of chloroform which interfere
with the subsequent crystallization
7. Dissolve the residue in 50 cc (total) of 95%
ethanol.
8. Cool the solution to any 10°C and add a
little H_2O slowly. This is done to re-
duce the solubility but not enough to
cause the precipitation of the product
as an oil.
9. Add a few crystals of seed to obtain the
pure crystallized nitro-chloro-pyridine and
10. Filter the crystals.
Dissolve the crystals in 50 cc of 95%
aqueous ethanol
11. Cool to 10°C
and add a little water
12. Add a few seed crystals to obtain a pure
13. Filter the pure crystallized material
Dissolve the crystals in 2 lts of ethanol

15. Evaporate the ethanol and H_2O [illegible]
(50 °C) from 10 to 6 [illegible]
16. cool the [illegible] to 10 °C
17. add a little H_2O
18. add a few seed crystals to obtain a [illegible]
19. filter the crystals
20. Recrystallize the crystals in [illegible] of hot ethanol
21. cool to 10 °C
22. add a little H_2O
23. add a few seed crystals to obtain a [illegible]
24. filter the crystals
25. Dissolve the crystals in 30 mL of ethanol and add the [illegible] to the

pg. 14

Yield = 6.7g



3-Cyano-4-ethoxycarbonyl-5-nitro-6-methyl-2-oxo-pyridine

M.W. 225.6

m.p. 47°-49°C

4-Aminomethyl-5-cyano-6-methyl-2-oxo-pyridine

M.W. 225.6

m.p. 190°C

To the 2.2 gm of 3-cyano-4-carboxyethyl-5-nitro-6-methyl-2-oxo-pyridine already dissolved in 300 cc of alcohol added 0.5 gm of Pt catalyst.

Pass in H_2 at a pressure of 3 atmosphere for 1½ hr. 3 mole of H_2 (≈ 0.52 gm) is absorbed.

Cool the mixture a crop of crystals is obtained.

Decant the mother liquor.

Extract the crystalline cpd with 50 cc portion of hot alcohol to dissolve the 4-amino-6-methyl-2-oxo-pyridine cpd. (Possibly this extraction may not be necessary)

Evaporate the alcohol to 150 cc

Cool the solution to 11°C, crystals form

Evaporate the mother liquor from (4) to dryness at 70°C

9. Cool the saturated mother liquor to 10°C to
crystallize
10. Filter the crystals
11. Extract the crystals with cold water portions
of 10 ml ethanol
12. Evaporate the ethanol extract to 5 ml
13. Cool the ethanol extract to 10°C crystallize
from
14. Combine the crystal ethanol mixture
from 7 and "13" and filter
15. Dry the crystals in air

2. Add to heat a mixture of [illegible] until
3. mole (= 0.70 gm) are dissolved.
4. Filter out the catalyst.
5. Concentrate the solution to only 100 cc. under
6. vacuum.
7. add 100 cc. of ethanol to precipitate the
8. NaCl.
9. Filter out the NaCl.
10. add 200 cc of ethanol containing 7.0 gm
11. of picric acid.
12. add a few seed crystals of the dipicrate
13. ammonia product and to yield a crop of
14. crystals on standing for 6 hrs.
15. Filter the crystals
16. Dissolve the crystals in 500 cc of 70% ethanol
17. evaporate the solution to only 100 cc.
18. cool the solution to 10°C to obtain a crop
19. of crystals
20. Filter the crystals
21. Dry the crystals in air.

7. Add 150 cc of acetone and a few crystals of Dihydrochloride - Ethoxy - Diamine and stand for 3 hrs till crystallization is complete

8. Filter off the crystals

9. Wash twice with 25 cc portions of acetone

10. Dissolve the crystals in 150 cc of a mixture of 75 cc acetone + 75 cc absolute ethanol

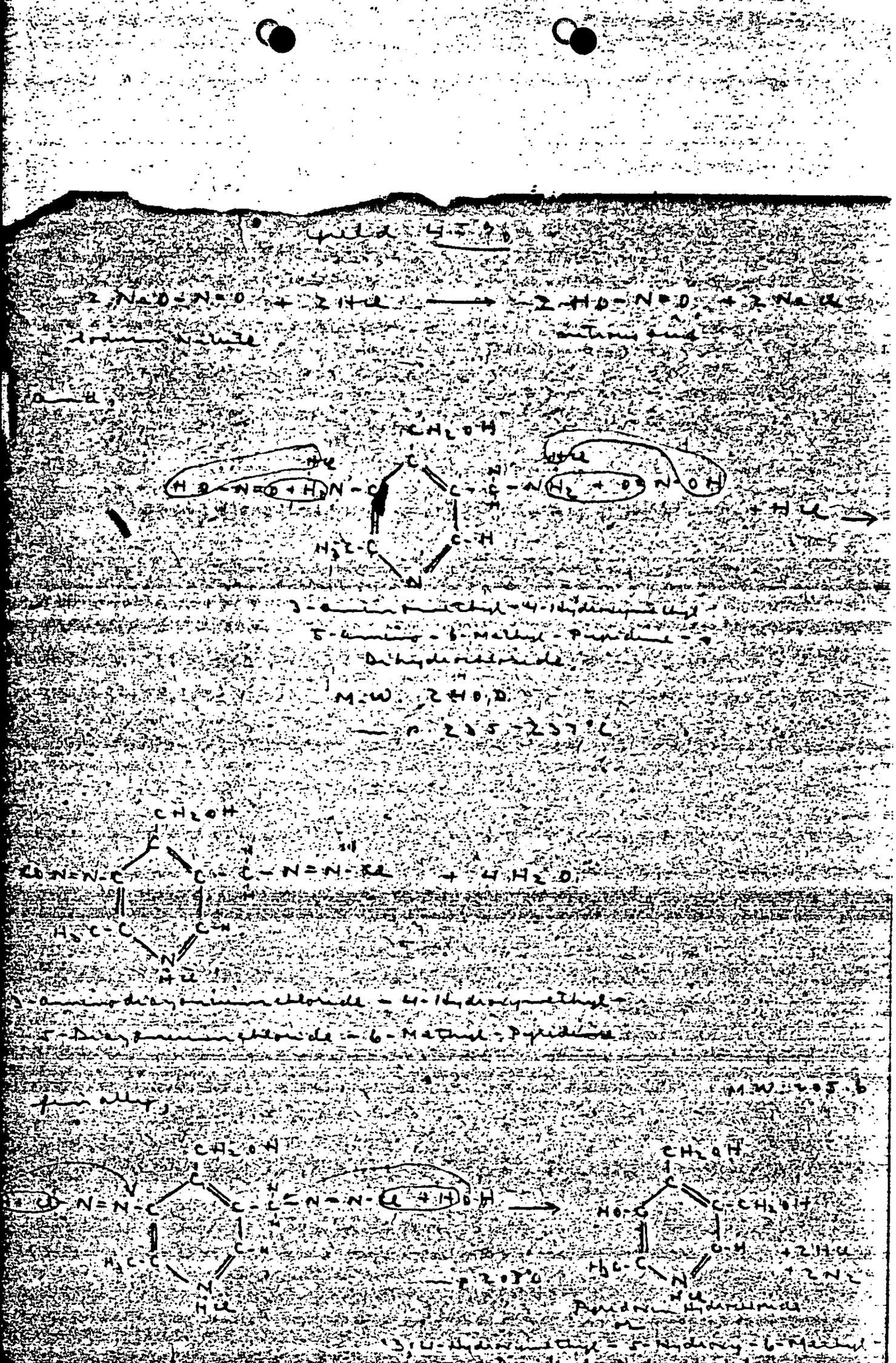
11. Evaporate the solution to dryness

12. Cool to 10°C

13. Add 150 cc of acetone at 10°C and a few crystals of Dihydrochloride - Ethoxy - Diamine and stand for 3 hrs till crystallization is complete

14. Filter the crystals

15. Dry the crystals in air



1. Dissolve [illegible] in [illegible] 5 cc methanol, [illegible] 22 cc of H_2O

2. Add the hydrochloric acid to [illegible] 2.24 gm of $NaHCO_3$ dissolved in 45 cc of 5% NH_4 ($= 9.1$ cc of 31% NH_4) at 95°C (20°F)

3. Concentrate the solution to dryness under reduced pressure (Note - The solution will foam)

4. Wash the residue with one 5 cc portion of acetone to remove most of the yellow color (Note - The vitamin B_{12} is only slightly soluble in acetone)

5. Extract the Vitamin B_{12} with four 11 cc washes of hot absolute ethanol

6. To the alcohol soln. of the Vitamin B_{12}, add 0.075 gm of activated carbon

7. Filter the soln.

8. Concentrate the alcohol soln. to any 2 cc

9. Cool the soln. to 5°C

10. Add 10 cc of acetone to precipitate the Vitamin B_{12}

11. Filter the crystals

12. Wash the with 2 cc of acetone at 5°C

13. Dry the Vitamin B_{12} crystals

Yield = 75%

2-cyanoethyl-5-amino-6-methyl-pyridine-dihydrochloride

M.W. 230.9

m.p. 195°C

5-amino-6-methyl-pyridine-3-HCl

M.W. 240.9

m.p. 235-237°C

Reactants: 4 gr 2.24 mol of 2-cyanoethyl-5-amino-6-methyl-pyridine-3-HCl

add

34 cc of 2.5 NH4Cl (= 2.9 cc of 36.9% HCl)

2. Heat in a bomb tube at 130°C (266°F) for 24 hrs.

3. Cool to 90°C (176°F).

4. add 0.2 gm of activated carbon

5. Filter the mixture.

6. Concentrate the solution to dryness

7. Dissolve the residue in 25 cc of a mixture of 25 cc of ethanol + 0 cc of water

8. Concentrate the solution to 8 cc.

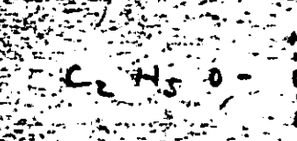
9. Cool the solution to 10°C; crystals form

10. Filter the crystals

11. Dry the crystals

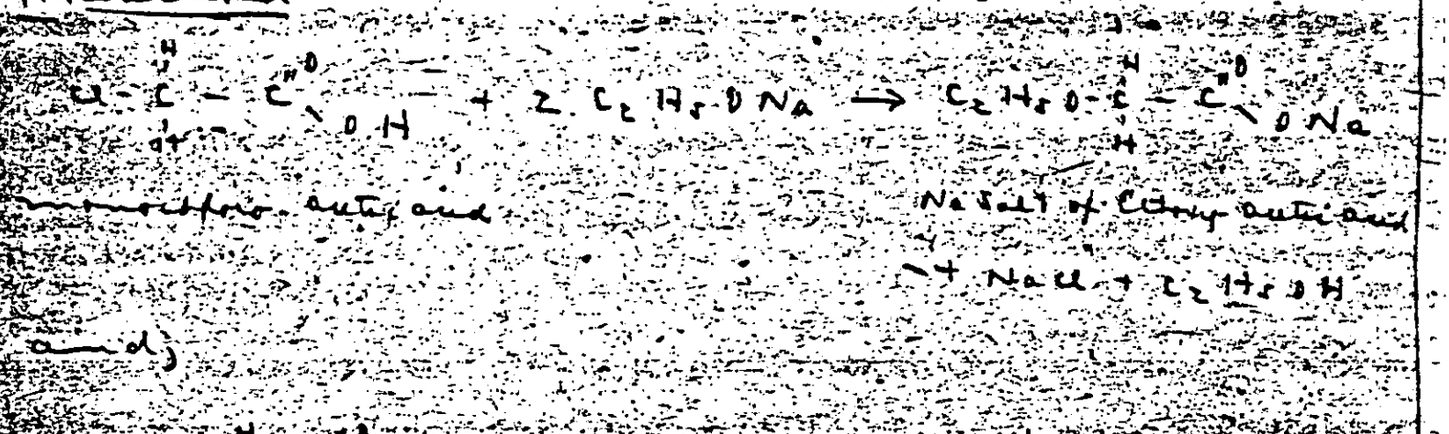
Step 1

monochloro acetic acid



Ethyl chloro acetate

1. Reaction

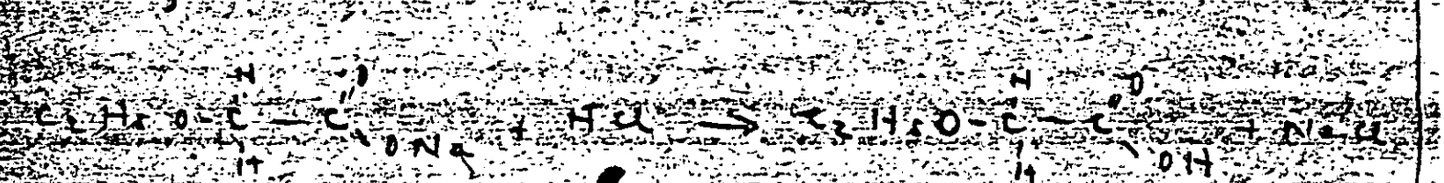


monochloro acetic acid

Na salt of Ethyl acetic acid

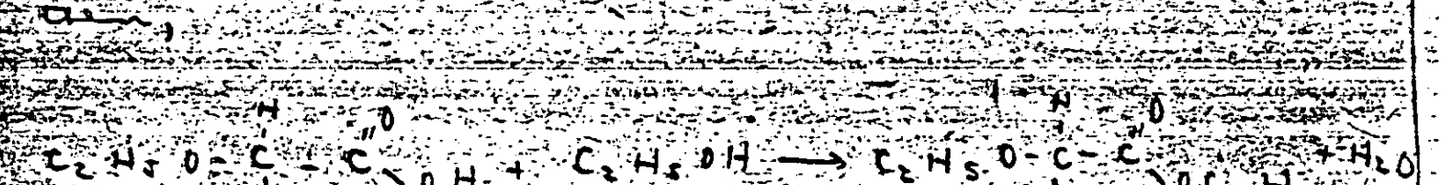
+ NaCl + C_2H_5OH

and



Ethyl acetic acid

Then



Ethyl chloro acetate

2. Reactants

monochloro acetic acid

absolute alcohol

Sodium metal

3. Reagents

Hydrochloric acid (3 to 1)

Hydrochloric acid 1 dm

Sodium carbonate

4. Yield

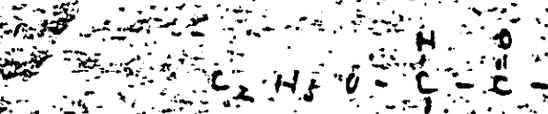
5 B 70

5. Unit operations

1 A_{20} - B_2 - F_5 - D_3 - E_3 - G_1 - H_2 - V_{16} - L_1 - N_1 - P_{20}

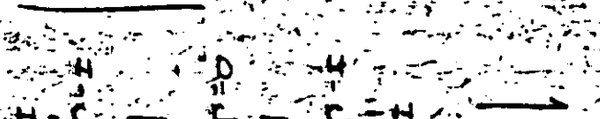
6. Solvents

Ethyl Ether



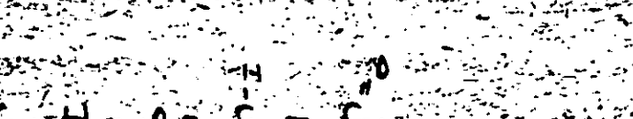
Ethoxy - acetyl - acetone

1. Reaction

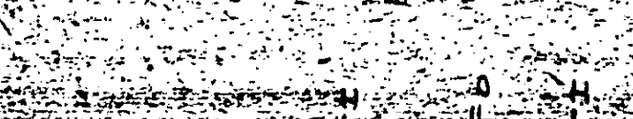


acetone

and

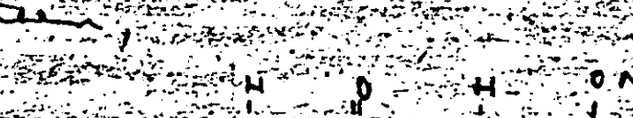


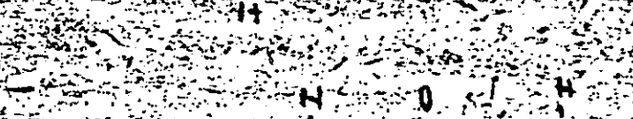
Ethoxy - Ethyl acetate



Na salt of Ethoxy - acetyl - acetone (enol form)

Acetone





Ethoxy - acetyl - acetone

Step 2

2. Reactants

ethoxy-ethyl acetate

acetoxol

sodium

3. Reagents

acetic acid

cupric sulfate

sulfuric acid

4. Yield

3 2 %

5. Unit operations

$A_{19} - B_3 - C_3 - D_2 - H_1 - J_{12} - L_3 - N_3 - P_{20}$

6. Solvents

Benzene

Ethyl ether

Ethyl alcohol (absolute)

Exp. C-1

Date

monochloro-acetic acid

$N\equiv C-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-OC_2H_5$

Cyano-ethyl acetate

1. Reaction

$2Cl-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-OH + Na_2CO_3 \rightarrow 2Cl-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-ONa + H_2O + CO_2$

monochloro-acetic acid

$2Cl-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-ONa + 2NaCN \rightarrow 2N\equiv C-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-ONa + 2NaCl$

Na salt of Cyano-acetic acid

then

$2N\equiv C-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-ONa + 2HCl \rightarrow 2N\equiv C-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-OH + 2NaCl$

Cyano-acetic acid

finally

$2N\equiv C-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-OH + 2C_2H_5OH \xrightarrow[\text{absolute alcohol}]{H_2SO_4} 2N\equiv C-\underset{H}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-OC_2H_5 + 2H_2O$

Cyano-ethyl acetate

2. Reactants

m-nitro-anisic acid

Iodine, Cyanide

Ethyl alcohol (absolute)

3. Reagents

Sodium carbonate

Hydrochloric acid

Sulphuric acid

4. Yield

5. Unit operations

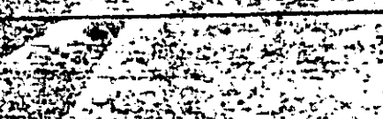
$A_{18} - B_3 - C_8 - D_3 - E_1 - H_3 - J_{12} - L_2 - P_{15}$

6. Solvents

Ethyl alcohol (95%)

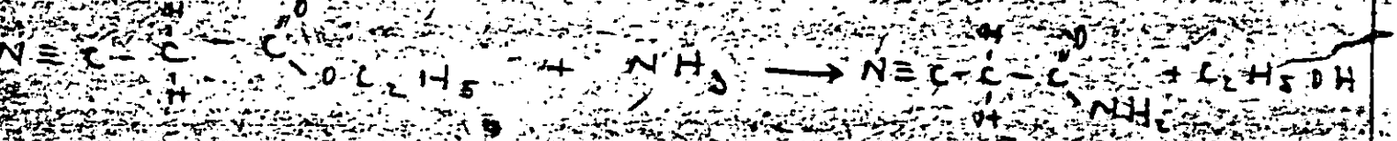
Benzene

Exp. 2 — 2



Cyanoacetamide

1. Reaction



Cyano-ethyl acetate — Cyanoacetamide

2. Reactants

Cyano-ethyl acetate

ammonia (aqueous)

3. Reagents

None

4. Yield

87%

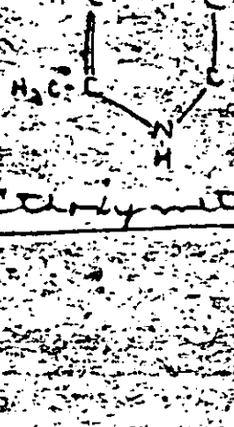
5. Unit operations

A6 - D1 - E4 - I2 - J2 - L2 - N2 - P7

6. Solvents

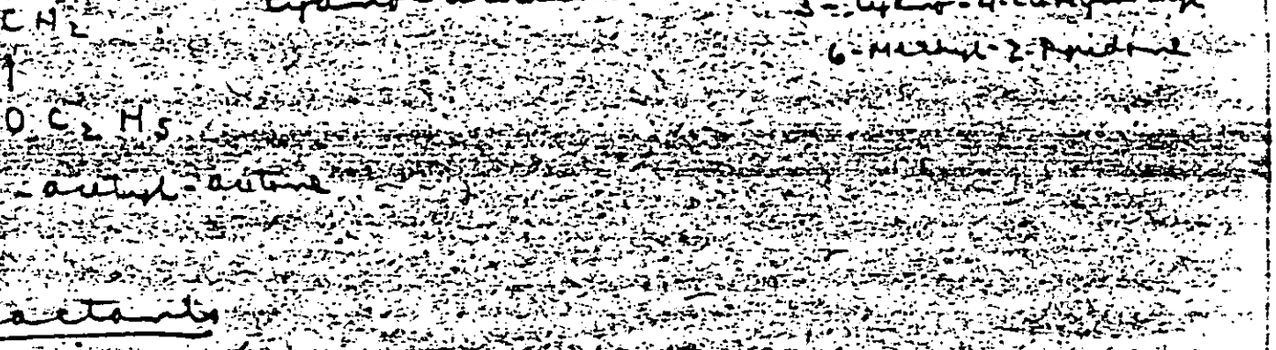
Ethyl alcohol

Exp 3 — p. 6



3-Cyano-4-Ethoxymethyl-6-Methyl-2-Pyridone

1. Reactants



Ethoxy-acetyl-acetone

Cyano-acetamide

3-Cyano-4-Ethoxymethyl-6-Methyl-2-Pyridone

2. Reactants

Ethoxy-acetyl-acetone

Cyano-acetamide

3. Reagents

None

4. Yield

5. Reaction operations

A2 - B1 - C4 - E1 - J3 - L2 - N2 - P3

6. Solvents

Ethyl alcohol (95%)

Piperidine